# The Genomic And Actionability Landscape Of Anal Carcinoma

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability

**Number of patients with data**

- WGS — 37
- RNASeq — 15
- Age, Sex — 10
- Biopsy site — 9
- Pretreatment — 7
- Treatment — 7
- Response — 6

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

- Chemo — 6 / 1 (17%)
- Multiple — 0 / 0
- Targeted — 0 / 0
- Hormonal — 0 / 0
- Immuno — 0 / 0
- Radio — 1 / 0
- Other — 0 / 0
- None or NA — 0 / 0

## Tumor Characteristics

Legend: ■ Anus  ■ Pan-Cancer

| Feature | Anus | Pan-Cancer |
|---|---|---|
| TMB High | 16% | 21% |
| MSI High | 0% | 2% |
| WGD | 43% | 56% |
| Diploid Proportion | 41% | 34% |
| GIE HLA LOH | 49% | 19% |
| GIE Overall | 62% | 26% |
| Viral Insertions | 73% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
64% / 55%

### Clonal mutation fraction
91% / 95%

### Tumor mutational burden
5.2 — 16% / 4.2 — 21% — High
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Anus | 12,958 | 1,121 | 183 | 141 |
| Pan-Cancer | 10,846 | 983 | 159 | 92 |

Number of variants vs Quantile

### Telomere Length
0.62 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
7 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.23 — 0% / 0.15 — 2% — Instable
MS indels per megabase

### Mean genome ploidy
2.2 / 2.6

### Aneuploidy Score
8 / 16

### % Copy number alteration
36% / 54%

### % Genome LOH
21% / 24%

## Processes Underlying Mutations

- APOBEC: 41%
- Chemical exposure: 12%
- DNA damage repair: 9%
- Ageing: 7%
- Tobacco: 5%
- UV light: 1%
- Unknown: 24%

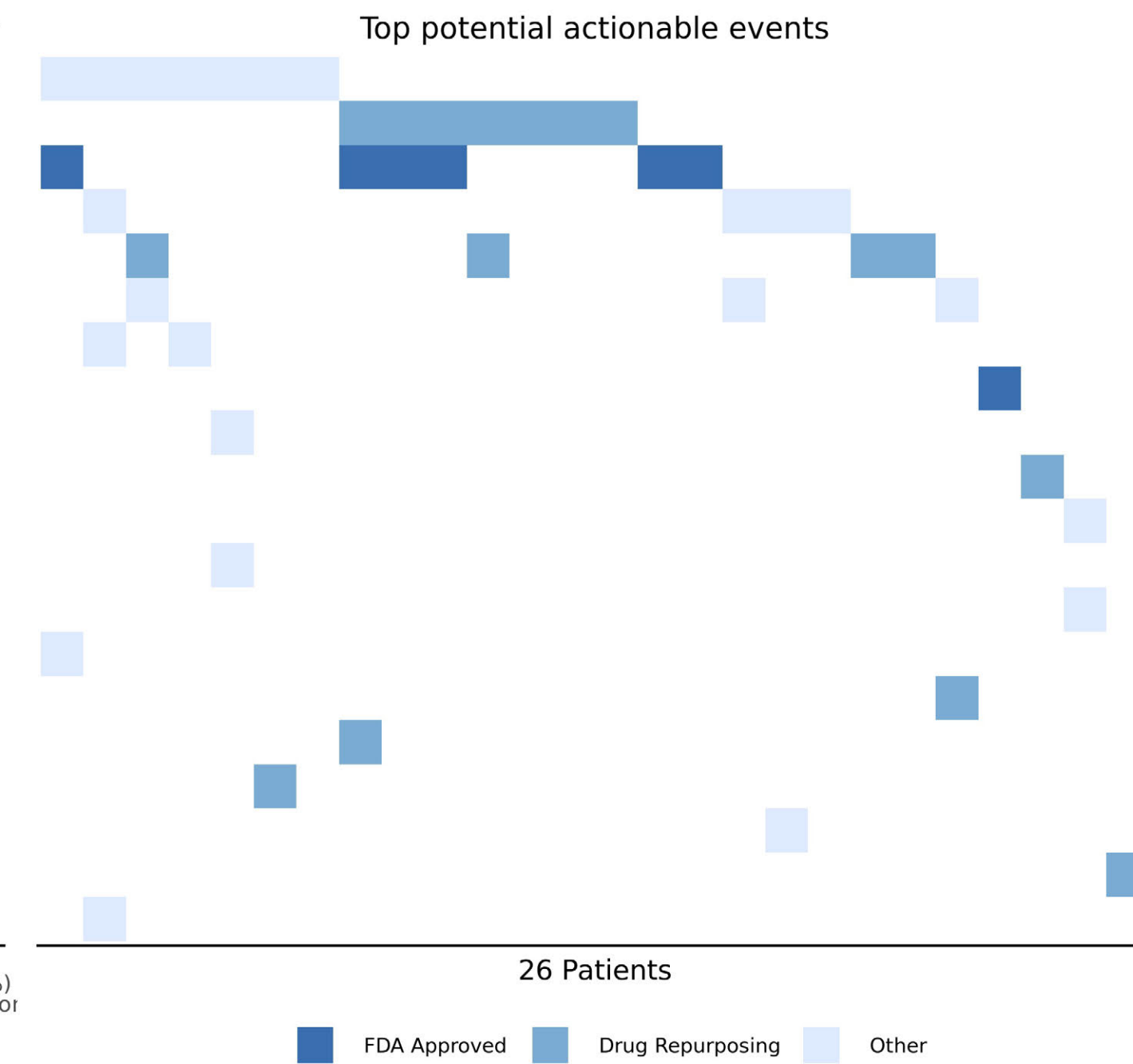**Anus** 37 Patients
**Pan-Cancer** 6790 Patients

Anal

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## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers

**Somatic drivers** (22% 6+ / 44% 6+; 76% 1-5 / 54% 1-5)

**Oncogenes** (27% None / 18% None; 8% 3+ / 32% 3+; 65% 1-2 / 50% 1-2)

**TSGs** (8% None / 6% None; 51% 3+ / 61% 3+; 41% 1-2 / 33% 1-2)

| Gene | Type | Anus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| PIK3CA | ONC | 22 | 13 | ▲ |
| TP53 | TSG | 22 | 55 | ▼ |
| CDKN2A | TSG | 19 | 25 | ▼ |
| APC | TSG | 14 | 14 | |
| FBXW7 | TSG | 14 | 2.8 | ▲ |
| KMT2C | TSG | 14 | 3.7 | ▲ |
| TGFBR2 | TSG | 14 | 2.7 | ▲ |
| KMT2D | TSG | 11 | 2.9 | ▲ |
| KRAS | TSG | 11 | 15 | |
| LRP1B | TSG | 11 | 2.1 | ▲ |
| PTEN | TSG | 11 | 14 | |
| B2M | TSG | 8.1 | 1.9 | ▲ |
| FAT1 | TSG | 8.1 | 1.5 | ▲ |
| RYR1 | ONC | 8.1 | 1.5 | ▲ |
| SMAD4 | TSG | 8.1 | 1.5 | ▲ |
| AR | ONC | 5.4 | 5.6 | |
| BRAF | ONC | 5.4 | 6.2 | |
| CASP8 | TSG | 5.4 | 0.6 | ▲ |
| DOCK8 | TSG | 5.4 | 0.6 | ▲ |
| EP300 | TSG | 5.4 | 1.3 | ▲ |
| FHIT | TSG | 5.4 | 4.3 | |
| HLA-B | TSG | 5.4 | 0.8 | ▲ |
| IL1RAPL1 | TSG | 5.4 | 0.8 | ▲ |
| KLF5 | ONC | 5.4 | 0.8 | ▲ |
| NOTCH1 | TSG | 5.4 | 1.3 | ▲ |
| PPP2R3B | TSG | 5.4 | 1 | ▲ |
| SRC | ONC | 5.4 | 0.5 | ▲ |
| STK11 | TSG | 5.4 | 4.1 | |
| TERT | ONC | 5.4 | 13 | ▼ |

**34 Patients**

Legend: ■ AMPLIFICATION  ■ DELETION  ■ MUTATION

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events

**Actionable** (30% None / 18% None; 14% 3+ / 26% 3+; 57% 1-2 / 56% 1-2)

**Best treatment option** (30% None / 18% None; 22% Oth / 14% Oth; 5% Exp; 30% Off / 28% Off; 19% FDA / 36% FDA)

| Gene | Anus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 19 | 24 | |
| PIK3CA | 19 | 13 | ▲ |
| TMB High | 16 | 21 | |
| KMT2D | 11 | 2.9 | ▲ |
| KRAS | 11 | 14 | |
| PTEN | 8.1 | 13 | ▼ |
| NOTCH1 | 5.4 | 0.2 | ▲ |
| BRAF | 2.7 | 5.9 | |
| CCND1 | 2.7 | 5.3 | |
| CHEK2 | 2.7 | 3 | |
| CTNNB1 | 2.7 | 2.7 | |
| EGFR | 2.7 | 5.1 | |
| ERBB3 | 2.7 | 0.5 | ▲ |
| ERBB4 | 2.7 | 0.5 | ▲ |
| FGFR3 | 2.7 | 1.2 | |
| FGFR3 - TACC3 fusion | 2.7 | 0.3 | ▲ |
| HRAS | 2.7 | 0.6 | ▲ |
| KDM5C | 2.7 | 0.6 | ▲ |
| MET | 2.7 | 1.7 | |
| NOTCH2 | 2.7 | 0 | ▲ |

**26 Patients**

Legend: ■ FDA Approved  ■ Drug Repurposing  ■ Other

## Germline Predisposition

### # Events / Summary / Top potential germline drivers

**Germline drivers** (81% None / 84% None; 19% 1+ / 16% 1+)

| Gene | Type | Anus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 5.4 | 3.2 | |
| MUTYH | TSG | 5.4 | 1.9 | |
| PMS2 | TSG | 2.7 | 0.5 | ▲ |
| RAD50 | TSG | 2.7 | 0.5 | ▲ |
| TP53 | TSG | 2.7 | 0.5 | ▲ |

**7 Patients**

Legend: ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved  ■ Drug Repurposing  ■ Experimental/Other Guidelines  □ Other  □ None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA | Rep | Exp/Other | None |
|---|---|---|---|---|
| WGS | 7 | 11 | 8 | 10 |
| Comprehensive 521 gene panel | 7 | 11 | 8 | 10 |
| Targeted 50 gene panel | 13 | 5 | — | 18 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | Total |
|---|---|---|---|
| WGS | 0.49 | 0.81 | 1.6 |
| Comprehensive 521 gene panel | 0.46 | 0.65 | 1.4 |
| Targeted 50 gene panel | 0.41 | | 0.7 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

- FDA Approved
- Drug Repurposing: Fusion — 1
- Experimental/Other Guidelines: Partial CN Loss — 1
- Other: Partial CN Loss — 6

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

- FDA Approved: TMB High — 6
- Drug Repurposing: Small Variant — 2; Fusion — 1
- Experimental/Other Guidelines: Full CN Gain — 2; Partial CN Loss — 1
- Other: Small Variant — 15; Partial CN Loss — 6; Full CN Loss — 1; Splice Site — 1

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Appendix Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

- WGS: 18
- RNASeq: 2
- Age, Sex: 2
- Biopsy site: 2
- Pretreatment: 2
- Treatment: 2
- Response: 2

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

- Chemo: 2 / 0
- Multiple: 0 / 0
- Targeted: 0 / 0
- Hormonal: 0 / 0
- Immuno: 0 / 0
- Radio: 0 / 0
- Other: 0 / 0
- None or NA: 0 / 0

## Tumor Characteristics

Legend: Appendix (dark blue), Pan-Cancer (grey)

- TMB High: 17% / 21%
- MSI High: 6% / 2%
- WGD: 56% / 56%
- Diploid Proportion: 42% / 34%
- GIE HLA LOH: 11% / 19%
- GIE Overall: 11% / 26%
- Viral Insertions: 0% / 3%
- HRD: 0% / 6%

## Mutational Landscape

- Tumor purity: 36% / 55%
- Clonal mutation fraction: 98% / 95%
- Tumor mutational burden: 3.8 (17% High) / 4.2 (21% High), TMB per Megabase

### Variant types (Number of variants vs Quantile)

- SNV: 10,846 / 9,556
- INDEL: 1,280 / 983
- Structural: 183 / 69
- MNV: 92 / 50

- Telomere Length: 1.3 / 0.82 — Log2 (Tumor/Germline length)
- VDJ CDR3 Sequences: 18 / 6 — Log2 (CDR3 + 1)
- Microsatellite instability: 0.33 (6% Instable) / 0.15 (2%) — MS indels per megabase

- Mean genome ploidy: 2.4 / 2.6
- Aneuploidy Score: 12 / 16
- % Copy number alteration: 39% / 54%
- % Genome LOH: 20% / 24%

## Processes Underlying Mutations

- DNA damage repair: 26%
- Ageing: 20%
- Chemical exposure: 18%
- UV light: 3%
- APOBEC: 2%
- Tobacco: 1%
- Unknown: 30%

Appendix 18 Patients / Pan-Cancer 6790 Patients

Appendix

## Copy Number Alteration Profile

Gene labels around chromosome ideogram include: KDM6A, EIF1AX, ZNF217, PRKACA, SMAD4, TYMS, SOX9, TGFBR2, CTNNB1, FHIT, IRS2, IL7R, LMBRD2, CTNNA1, CCND3, E2H2, MYC, KRAS, ATM, CCND1, CDKN2A, LHT1, MYC

## Cancer Driver Landscape

### # Events / Summary (Top cancer drivers)

| Gene | Type | Appendix (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|---|
| TP53 | TSG | 67 | 55 | ▲ |
| KRAS | ONC | 56 | 15 | ▲ |
| SMAD4 | TSG | 22 | 8 | |
| GNAS | ONC | 17 | 1.5 | ▲ |
| KDM6A | TSG | 17 | 3.7 | ▲ |
| NOTCH1 | TSG | 17 | 1.3 | ▲ |
| ATM | TSG | 11 | 2.9 | ▲ |
| BRAF | ONC | 11 | 6.2 | |
| RHOA | ONC | 11 | 0.5 | ▲ |
| SOX9 | TSG | 11 | 1.8 | ▲ |
| ACVR2A | TSG | 5.6 | 2 | |
| APC | TSG | 5.6 | 14 | ▼ |
| AR | ONC | 5.6 | 5.6 | |
| ARID1A | TSG | 5.6 | 6 | |
| CCND1 | ONC | 5.6 | 5.6 | |
| CCND3 | ONC | 5.6 | 0.8 | ▲ |
| CDKN2A | TSG | 5.6 | 25 | ▼ |
| CTNNA1 | TSG | 5.6 | 1 | |
| CTNNB1 | ONC | 5.6 | 2.9 | |
| CTNNB1_CTNNB1 | ONC | 5.6 | 0.3 | ▲ |
| EIF1AX | ONC | 5.6 | 0.6 | |
| ELF3 | TSG | 5.6 | 1.3 | ▲ |
| EP300 | TSG | 5.6 | 1.3 | |
| ERBB4 | ONC | 5.6 | 0.5 | |
| EZH2 | ONC | 5.6 | 0.9 | |
| FHIT | TSG | 5.6 | 4.3 | |
| IL7R | ONC | 5.6 | 0.9 | ▲ |
| IRS2 | ONC | 5.6 | 0.8 | ▲ |
| KMT2D | TSG | 5.6 | 2.9 | |

# Events (Somatic drivers): Appendix 6% None / 33% 6+ / 61% 1-5 ; Pan-Cancer None 44% 6+ / 1-5 54%

Oncogenes: Appendix 22% None / 28% 3+ / 50% 1-2 ; Pan-Cancer None 18% / 3+ 32% / 1-2 50%

TSGs: Appendix 11% None / 56% 3+ / 33% 1-2 ; Pan-Cancer None / 3+ 61% / 1-2 33%

17 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange), FUSION (light blue)

## Potentially Actionable Events

### Top potential actionable events

| Gene | Appendix (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|
| KRAS | 56 | 14 | |
| TMB High | 17 | 21 | ▲ |
| ATM | 11 | 3.5 | ▲ |
| BRAF | 11 | 5.9 | ▲ |
| AR | 5.6 | 2.8 | |
| BRCA1 | 5.6 | 1.3 | ▲ |
| CCND1 | 5.6 | 5.3 | |
| CDKN2A | 5.6 | 24 | ▼ |
| CHEK2 | 5.6 | 3 | |
| CTNNB1 | 5.6 | 2.7 | |
| ERBB4 | 5.6 | 0.5 | ▲ |
| KMT2D | 5.6 | 2.9 | |
| MSI High | 5.6 | 3.1 | |
| NOTCH1 | 5.6 | 0.2 | ▲ |
| PIK3CA | 5.6 | 13 | ▼ |
| PTEN | 5.6 | 13 | ▼ |
| RAD54L | 5.6 | 0.3 | ▲ |

Actionable # Events: Appendix 33% None / 26% 3+ / 33% 3+ / 33% 1-2 ; Pan-Cancer None 18% / 3+ 26% / 1-2 56%

Best treatment option: None 33%, Oth 14%, Exp, Off 33%, FDA 28% (Appendix); Pan-Cancer None, Oth, Off 28%, FDA 36%

12 Patients

Legend: FDA Approved (dark blue), Drug Repurposing (medium blue), Experimental/Other Guidelines (light blue), Other (pale blue)

## Germline Predisposition

### Top potential germline drivers

| Gene | Type | Appendix (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|---|
| BRCA1 | TSG | 5.6 | 1.1 | ▲ |
| CDKN2A | TSG | 5.6 | 0.2 | ▲ |
| CHEK2 | TSG | 5.6 | 3.2 | |
| MSH6 | TSG | 5.6 | 0.4 | ▲ |
| RAD54L | TSG | 5.6 | 0.4 | ▲ |

Germline drivers # Events: Appendix 78% None / 22% 1+ ; Pan-Cancer None 84% / 1+ 16%

4 Patients

Legend: SMALL_VARIANT (orange)

## WGS vs Panel Coverage

### Highest evidence level treatment option identified by test strategy

(# of patients in Hartwig database)

- WGS: FDA Approved 5, Drug Repurposing 6, Other 1, None 6
- Comprehensive 521 gene panel: 5, 6, 1, 6
- Targeted 50 gene panel: 3, 8, 1, 6

Legend: FDA Approved, Drug Repurposing, Other, None

### Average number of identified potentially actionable events identified by test strategy

(Average number of actionable events per patient)

- WGS: 0.33, 0.83, 0.56 → 1.9
- Comprehensive 521 gene panel: 0.33, 0.78, 0.44 → 1.7
- Targeted 50 gene panel: 0.56, → 0.9

### Top missed events by Comprehensive Panel vs WGS

- FDA Approved: (none)
- Drug Repurposing: Partial CN Loss 1
- Experimental/Other Guidelines: Small Variant 1
- Other: Partial CN Loss 1

(Number of Missed Events)

### Top missed events by Targeted Panel vs WGS

- FDA Approved: TMB High 3
- Drug Repurposing: Small Variant 2, Splice Site 2, Partial CN Loss 1
- Experimental/Other Guidelines: Full CN Gain 2
- Other: Small Variant 5, Splice Site 2, Partial CN Loss 1

(Number of Missed Events)

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the % (percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.
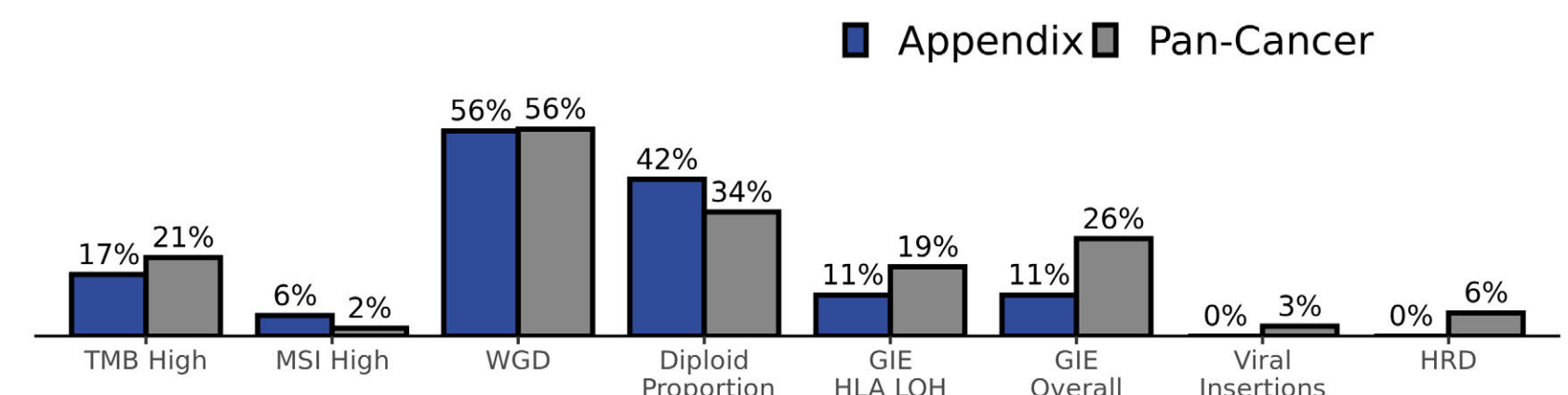
WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across
various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as
a baseline, and panel coverage determined by rules below.
 - Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High captured by targeted panel.
 - Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
 - Copy number: Events for panel genes with min copy number < 0.5 or max copy number > 6 assumed covered.
 - Other events: Fusions, HMZ (Homozygous) Distruptions, High inserts, HLA type assumed not captured by panels.
** See documentation for further details on the WGS vs Panel coverage study.

Acronym: APCA
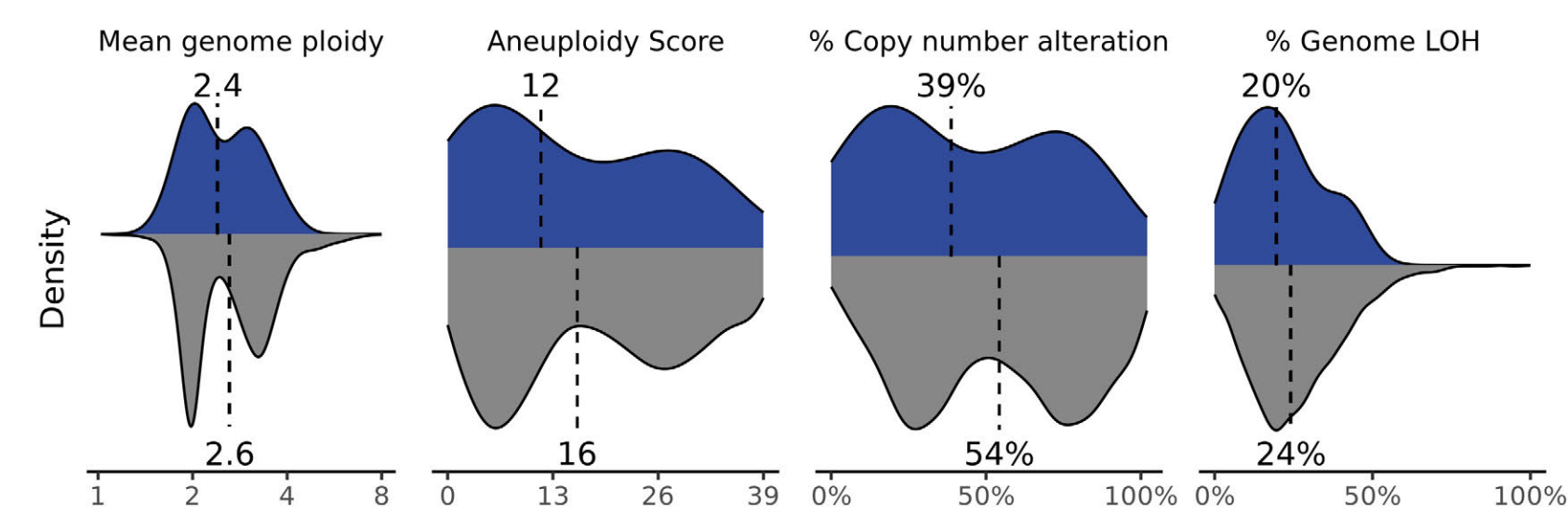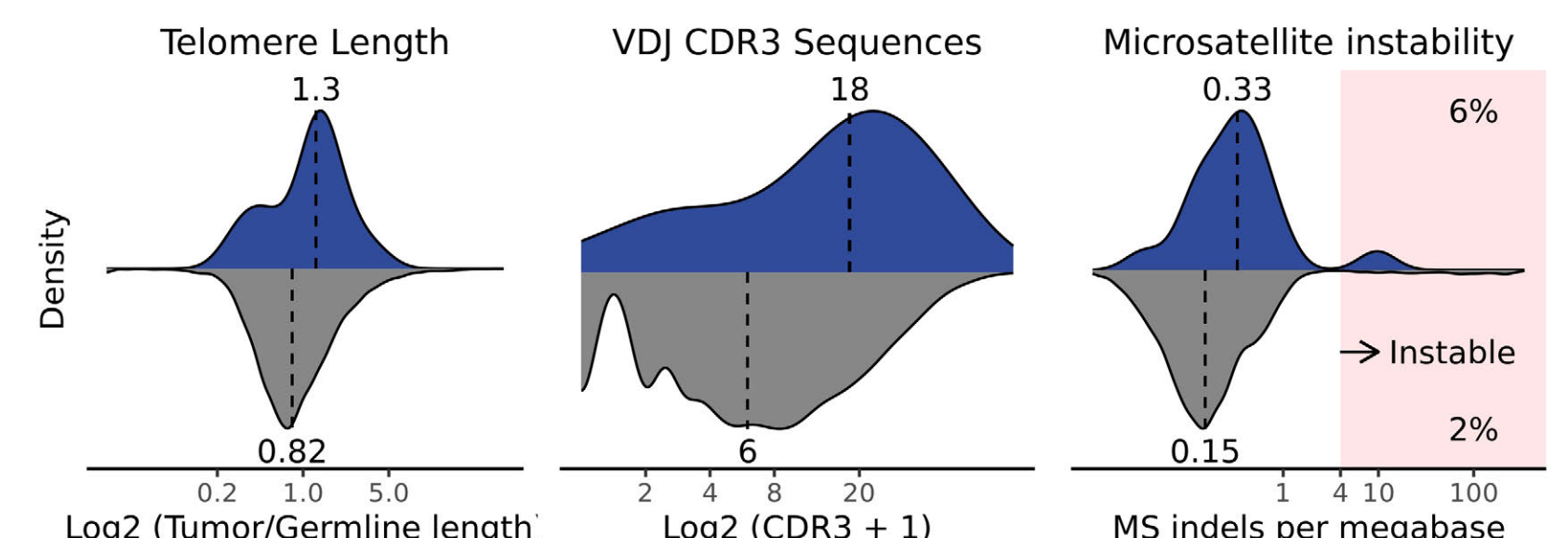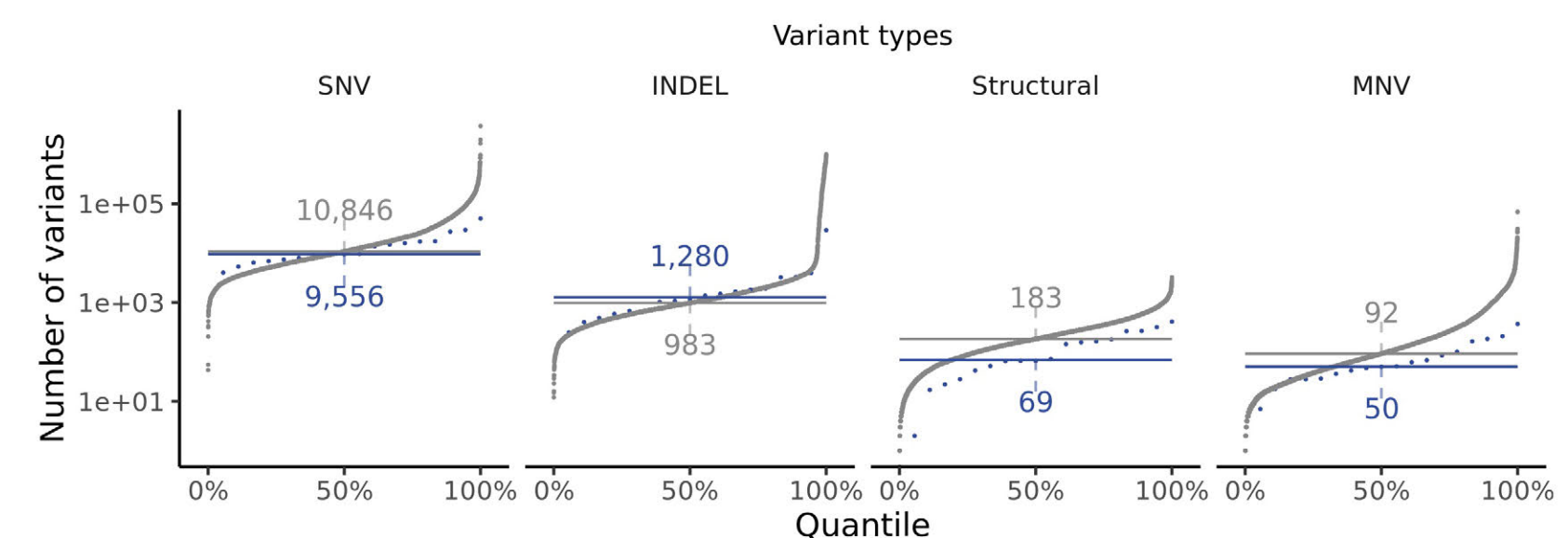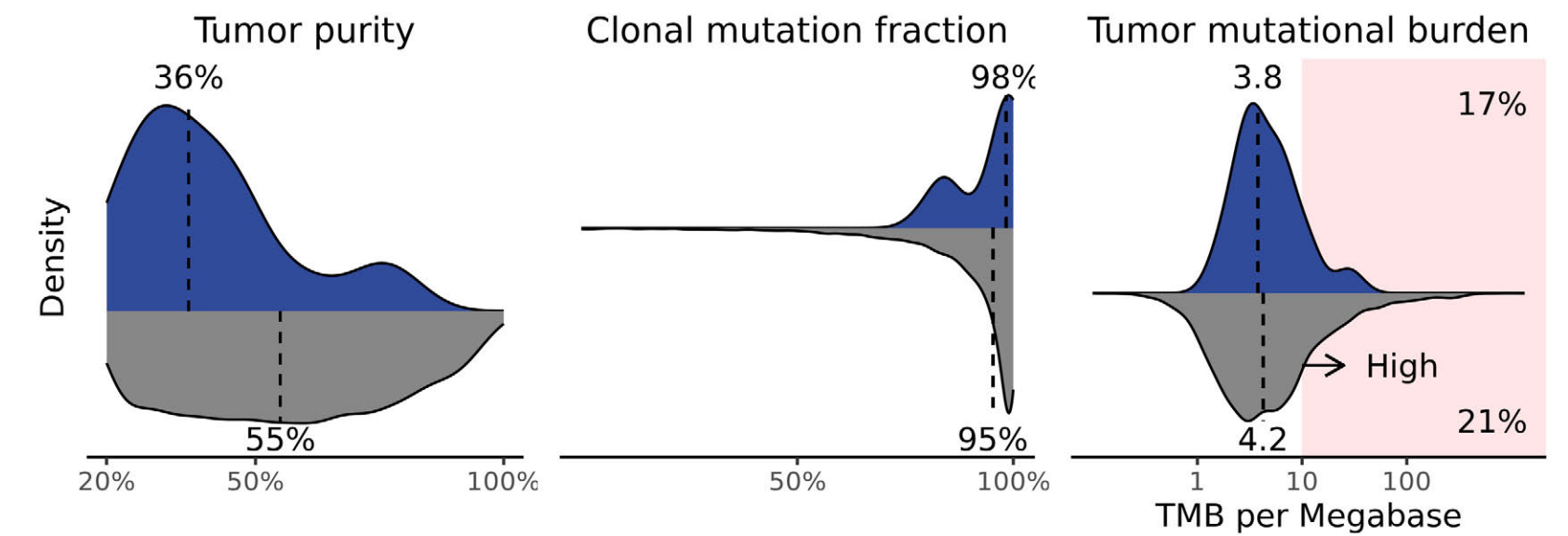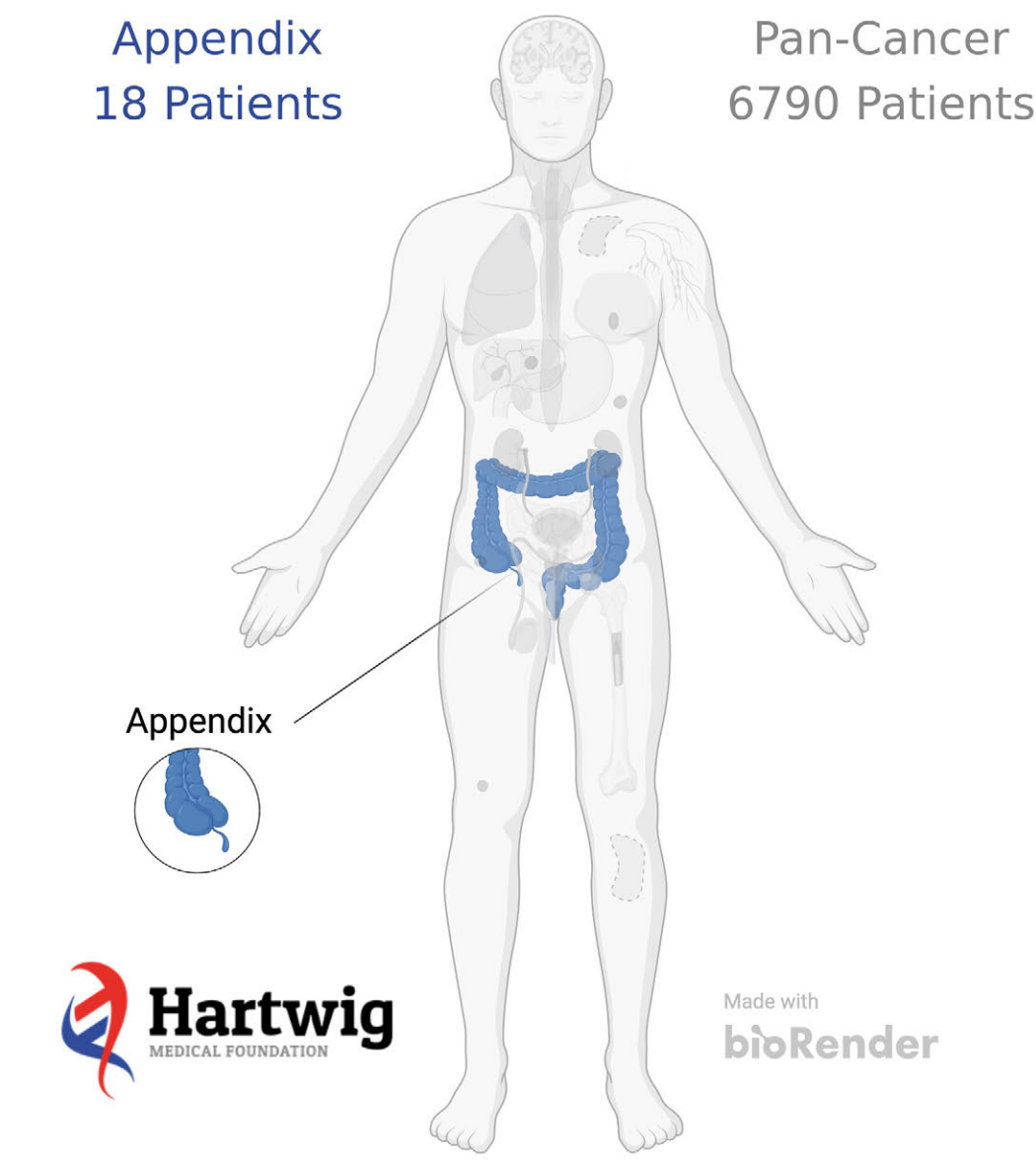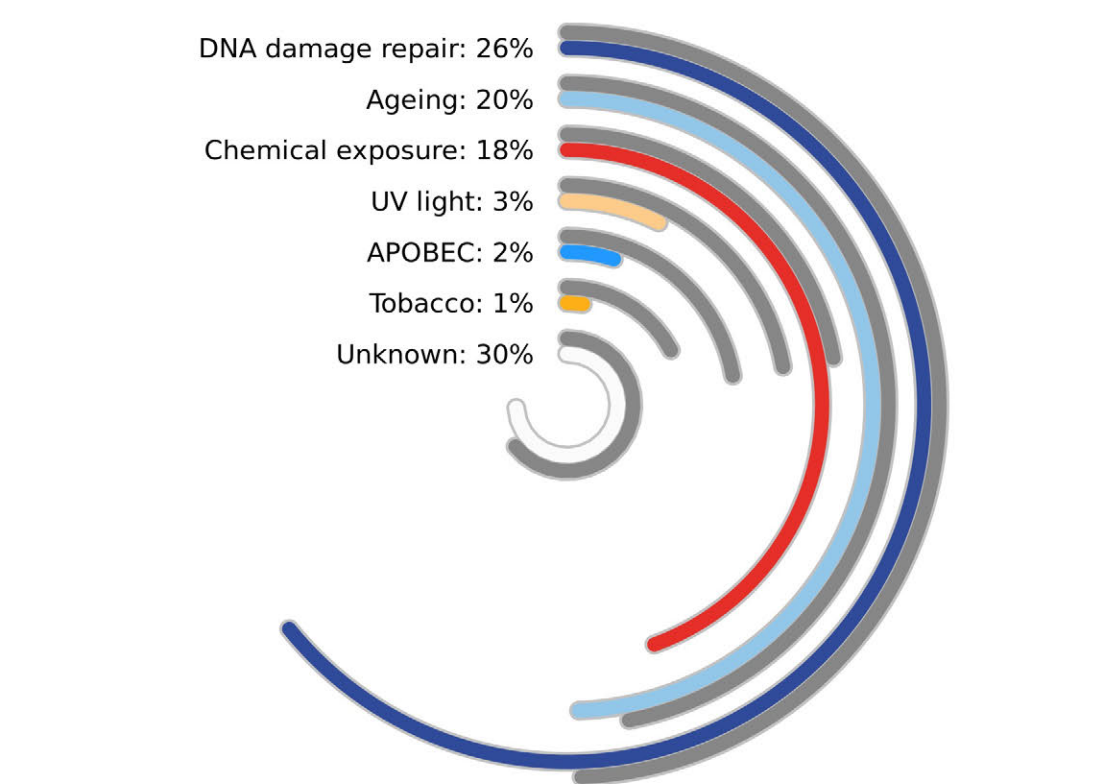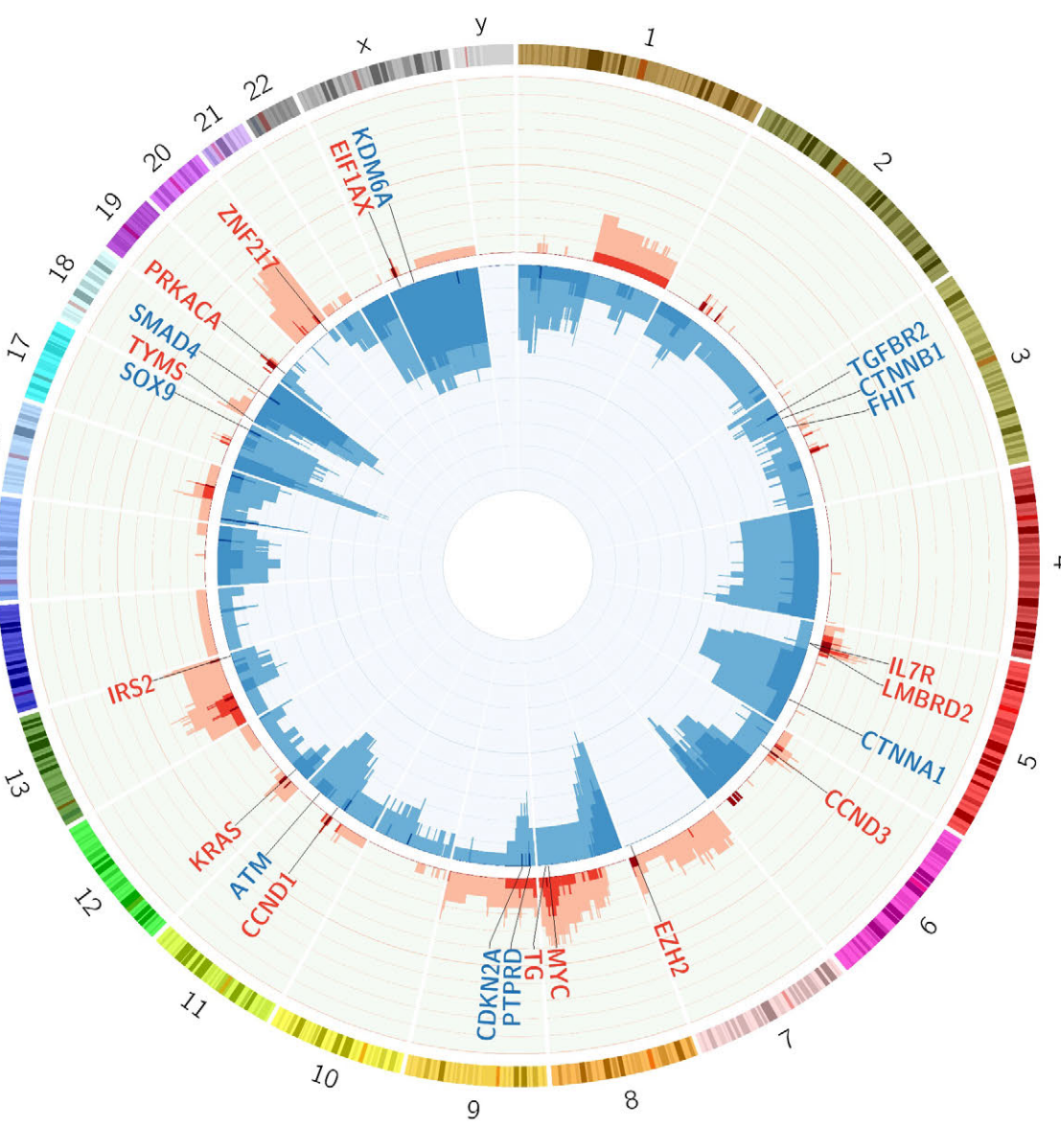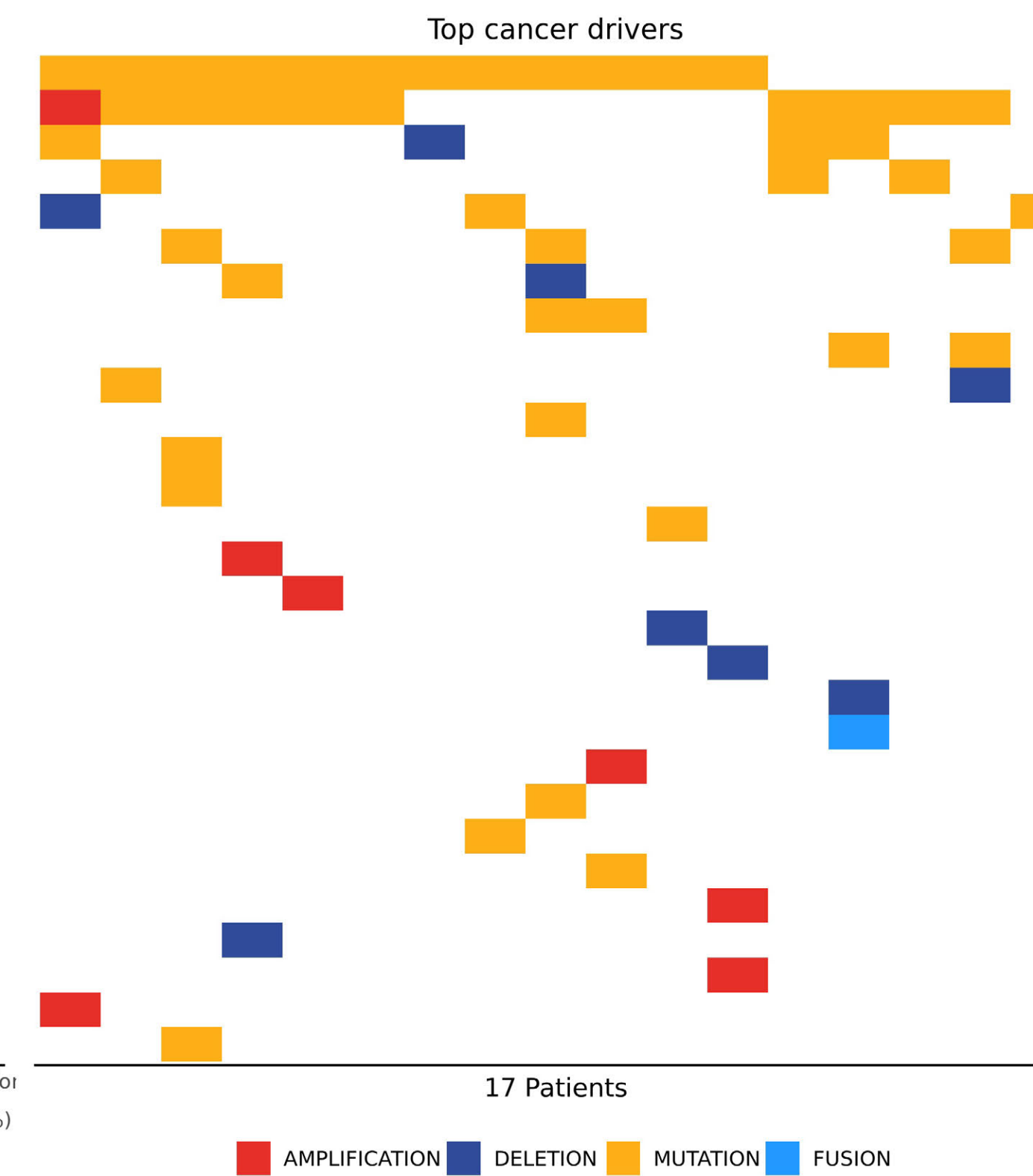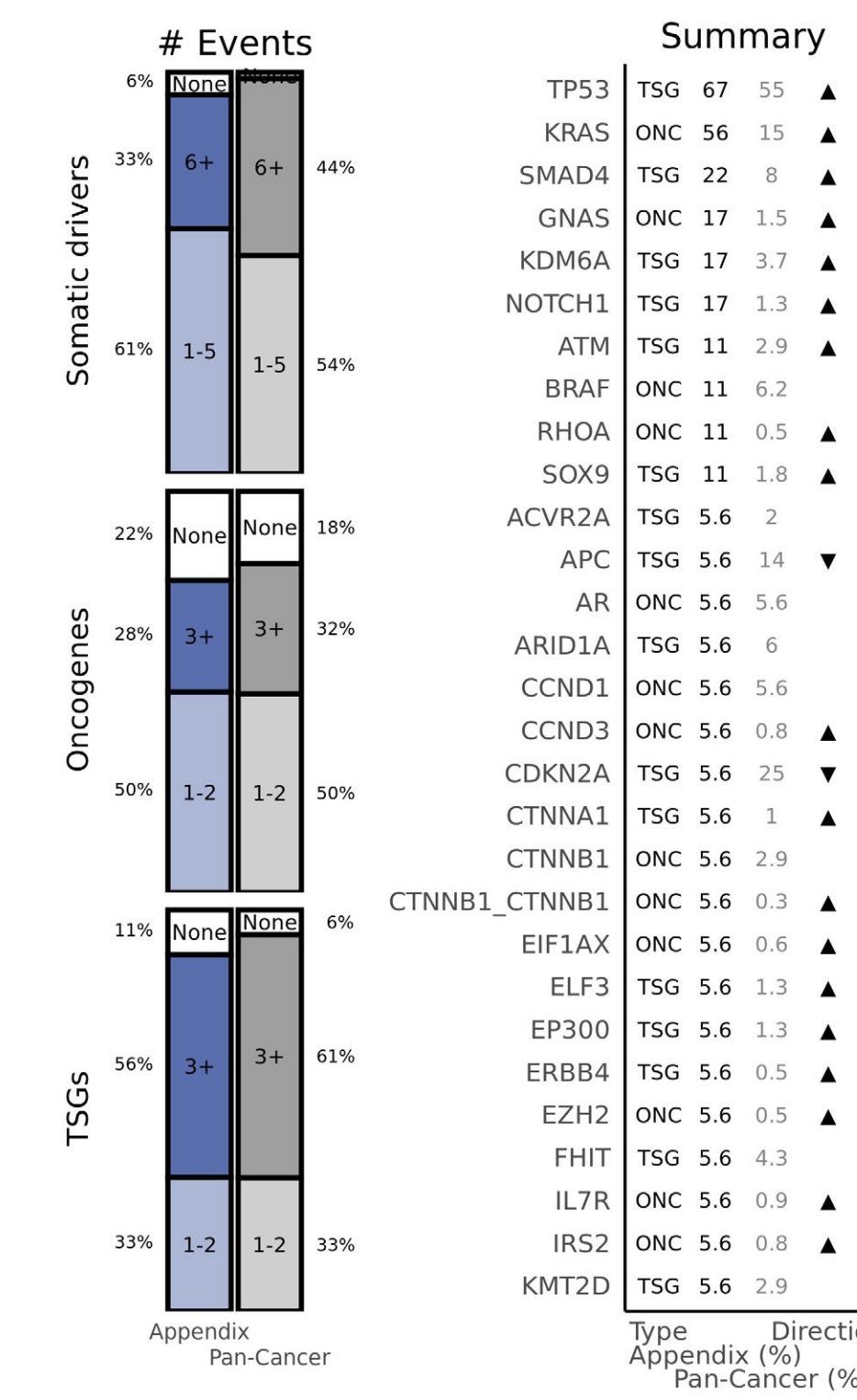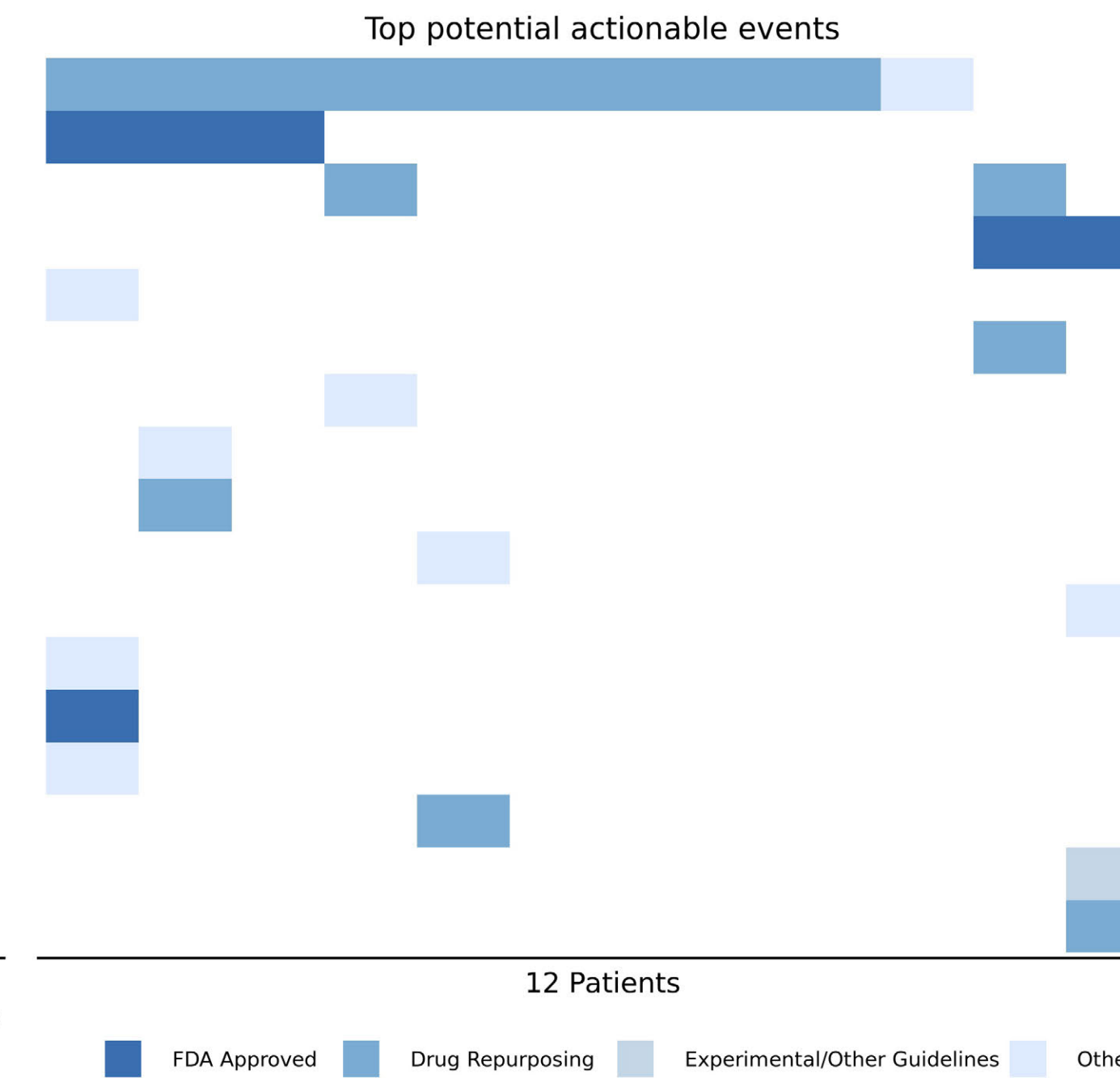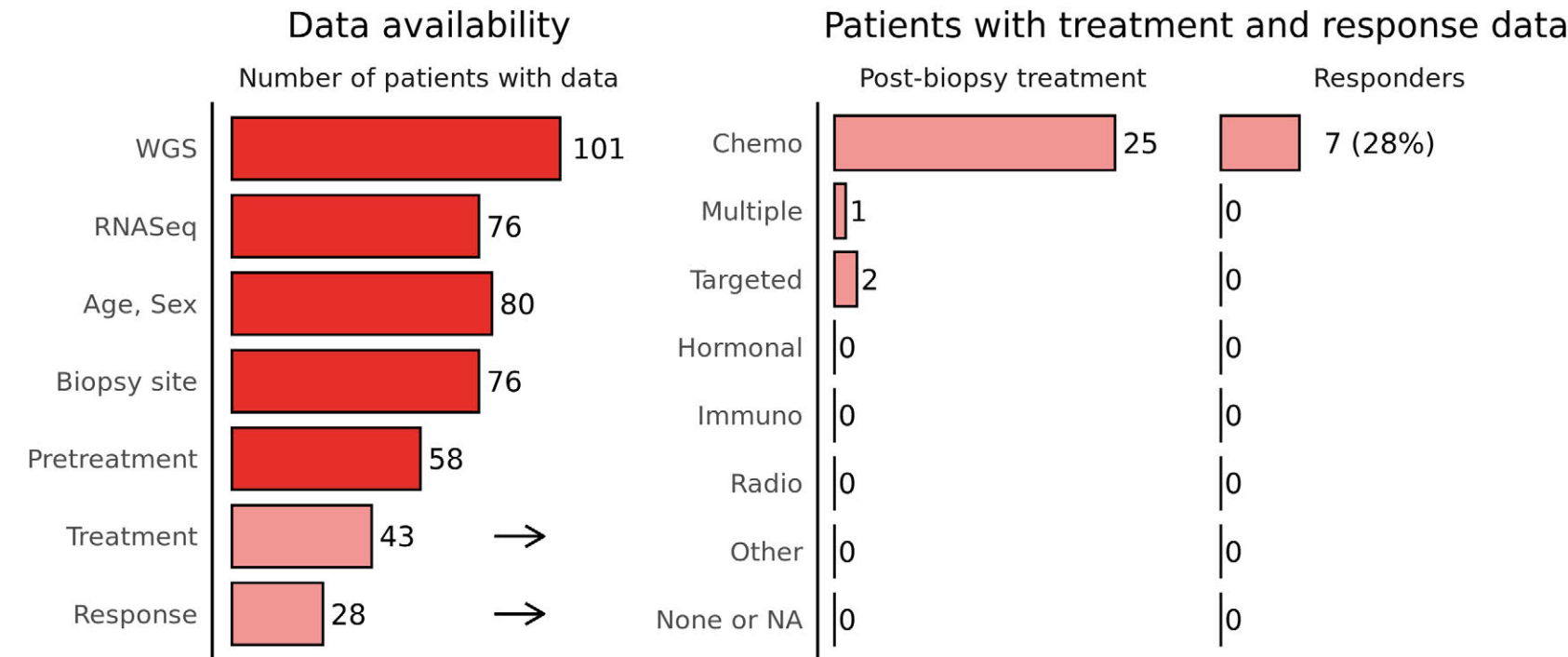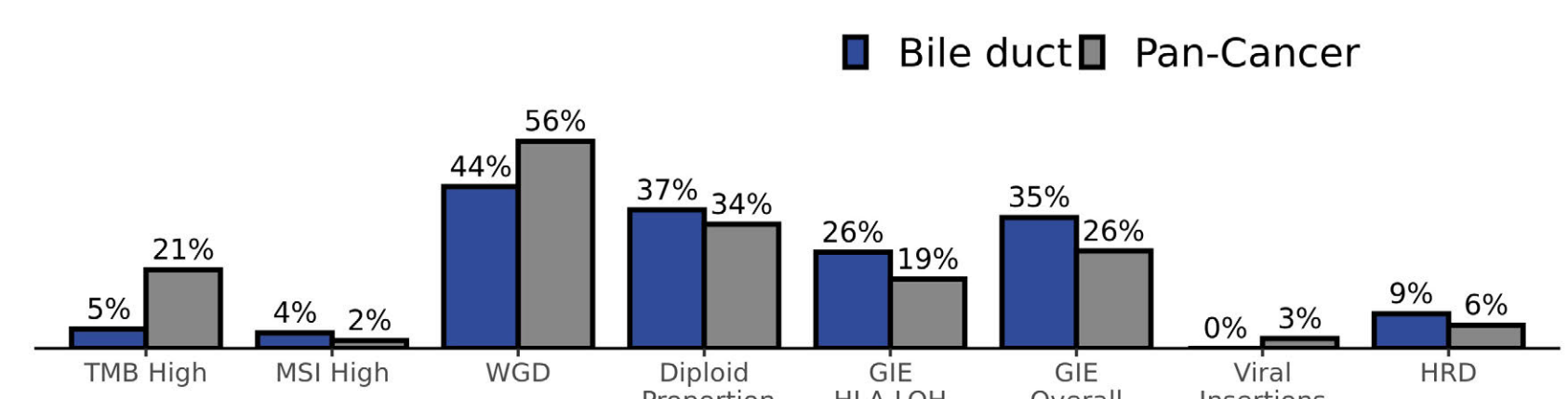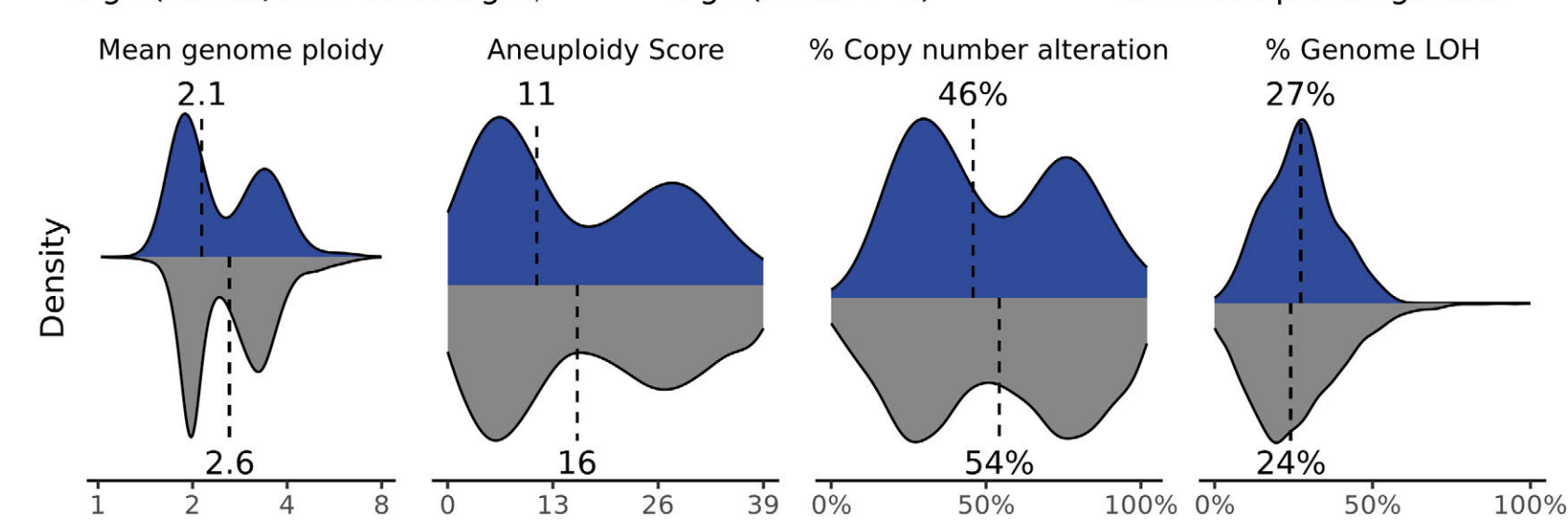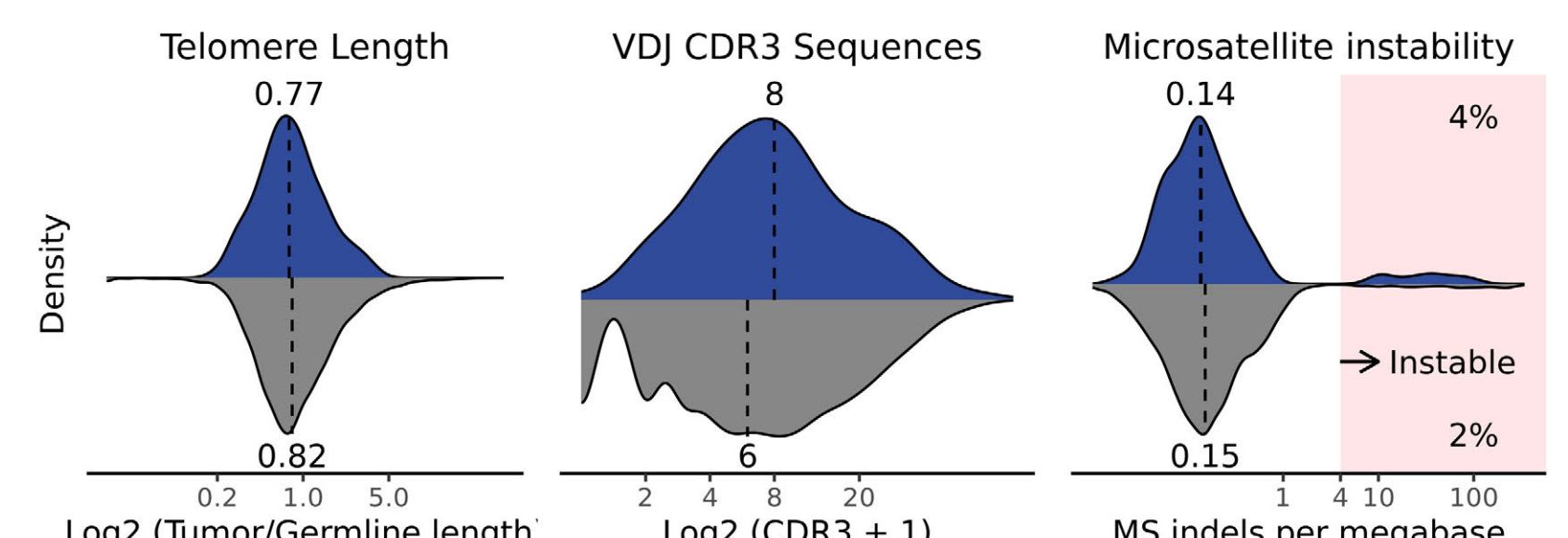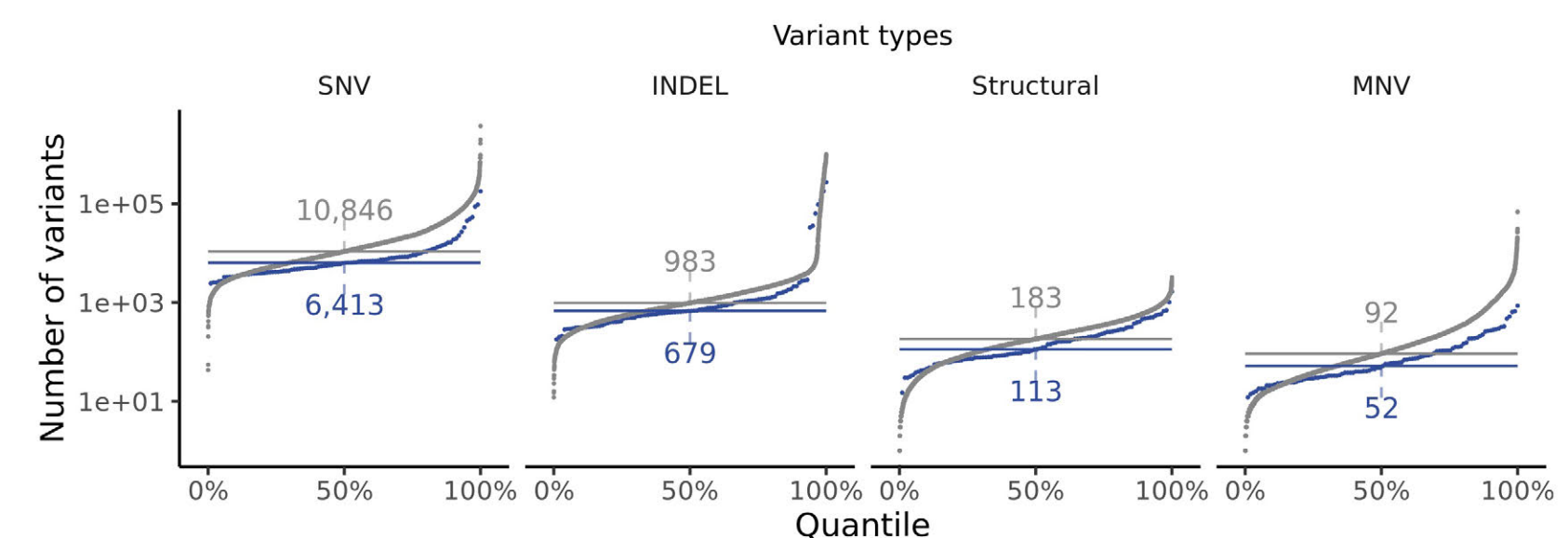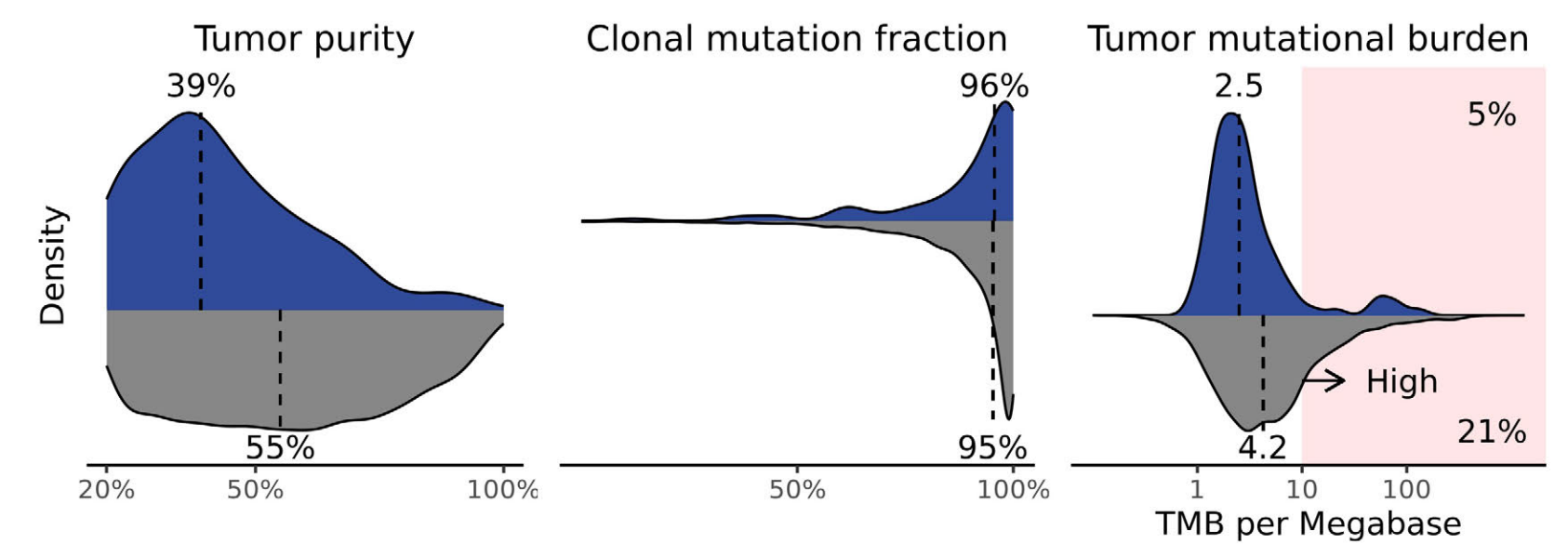DOIDs included: 3608, 3493, 4902
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# The Genomic And Actionability Landscape Of Cholangiocarcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 101 |
| RNASeq | 76 |
| Age, Sex | 80 |
| Biopsy site | 76 |
| Pretreatment | 58 |
| Treatment | 43 → |
| Response | 28 → |

### Patients with treatment and response data

**Post-biopsy treatment**

| | |
|---|---|
| Chemo | 25 |
| Multiple | 1 |
| Targeted | 2 |
| Hormonal | 0 |
| Immuno | 0 |
| Radio | 0 |
| Other | 0 |
| None or NA | 0 |

**Responders**: 7 (28%)

| | |
|---|---|
| Chemo | 7 (28%) |
| Multiple | 0 |
| Targeted | 0 |
| Hormonal | 0 |
| Immuno | 0 |
| Radio | 0 |
| Other | 0 |
| None or NA | 0 |

## Tumor Characteristics

Legend: Bile duct, Pan-Cancer

| | Bile duct | Pan-Cancer |
|---|---|---|
| TMB High | 5% | 21% |
| MSI High | 4% | 2% |
| WGD | 44% | 56% |
| Diploid Proportion | 37% | 34% |
| GIE HLA LOH | 26% | 19% |
| GIE Overall | 35% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 9% | 6% |

## Mutational Landscape

**Tumor purity** 39% / 55%
**Clonal mutation fraction** 96% / 95%
**Tumor mutational burden** 2.5 / 4.2 High 5% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Bile duct | 6,413 | 679 | 113 | 52 |

Number of variants vs Quantile

**Telomere Length** 0.77 / 0.82 — Log2 (Tumor/Germline length)
**VDJ CDR3 Sequences** 8 / 6 — Log2 (CDR3 + 1)
**Microsatellite instability** 0.14 / 0.15 Instable 4% / 2% — MS indels per megabase

**Mean genome ploidy** 2.1 / 2.6
**Aneuploidy Score** 11 / 16
**% Copy number alteration** 46% / 54%
**% Genome LOH** 27% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| DNA damage repair | 35% |
| Ageing | 20% |
| Chemical exposure | 11% |
| APOBEC | 4% |
| Tobacco | 2% |
| UV light | 2% |
| Unknown | 26% |

**Bile duct** — 101 Patients
**Pan-Cancer** — 6790 Patients
Bile duct

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## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers
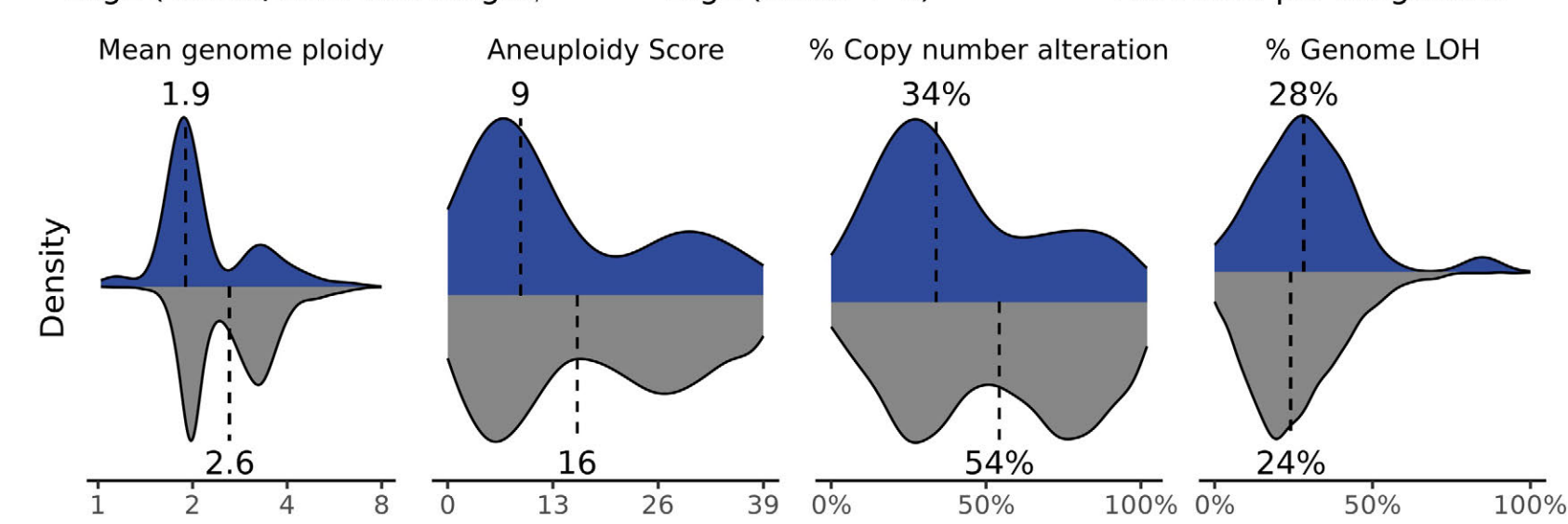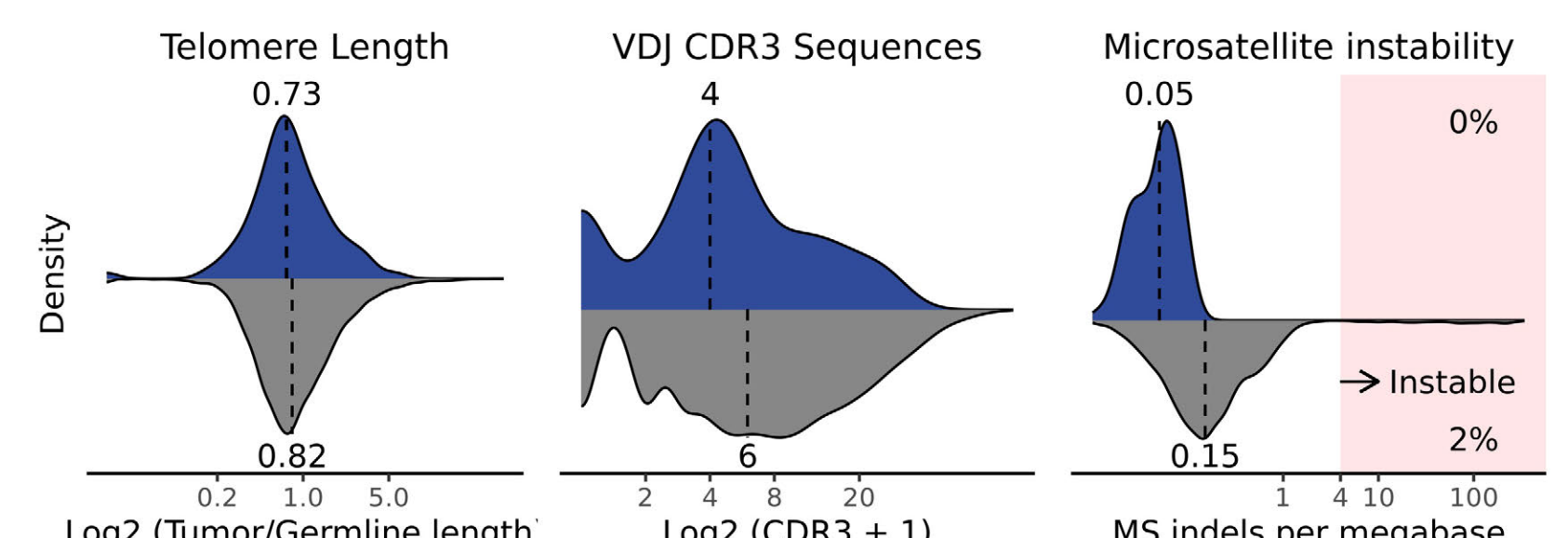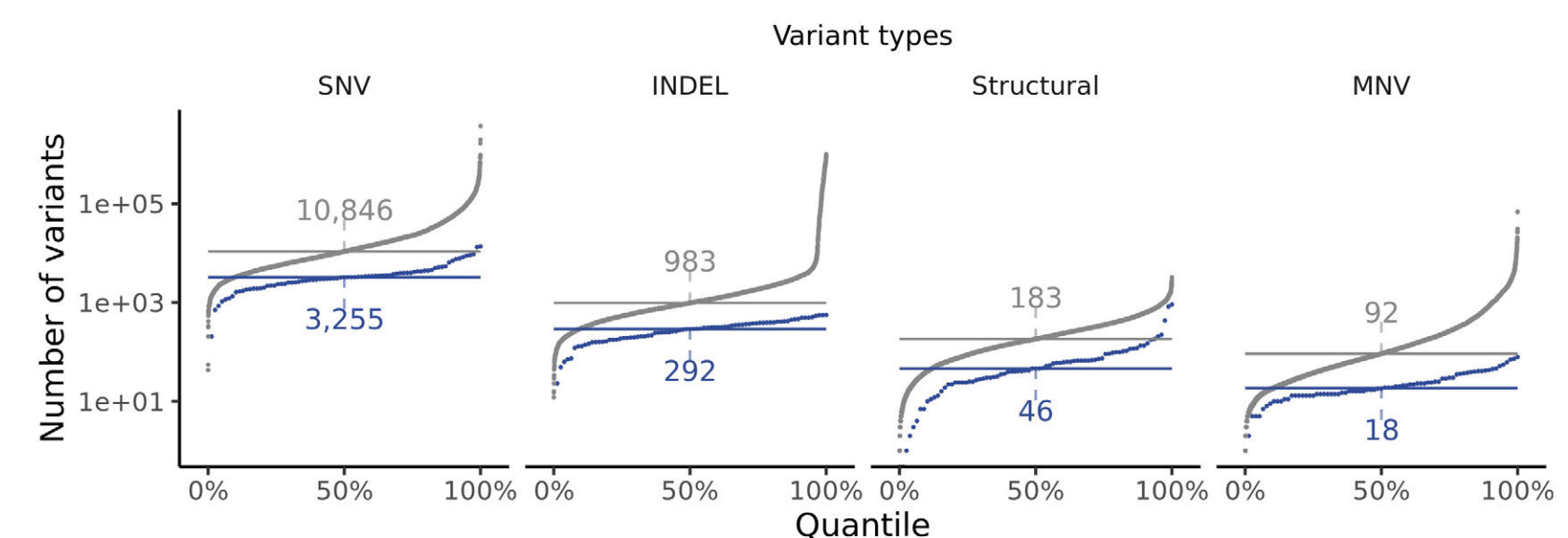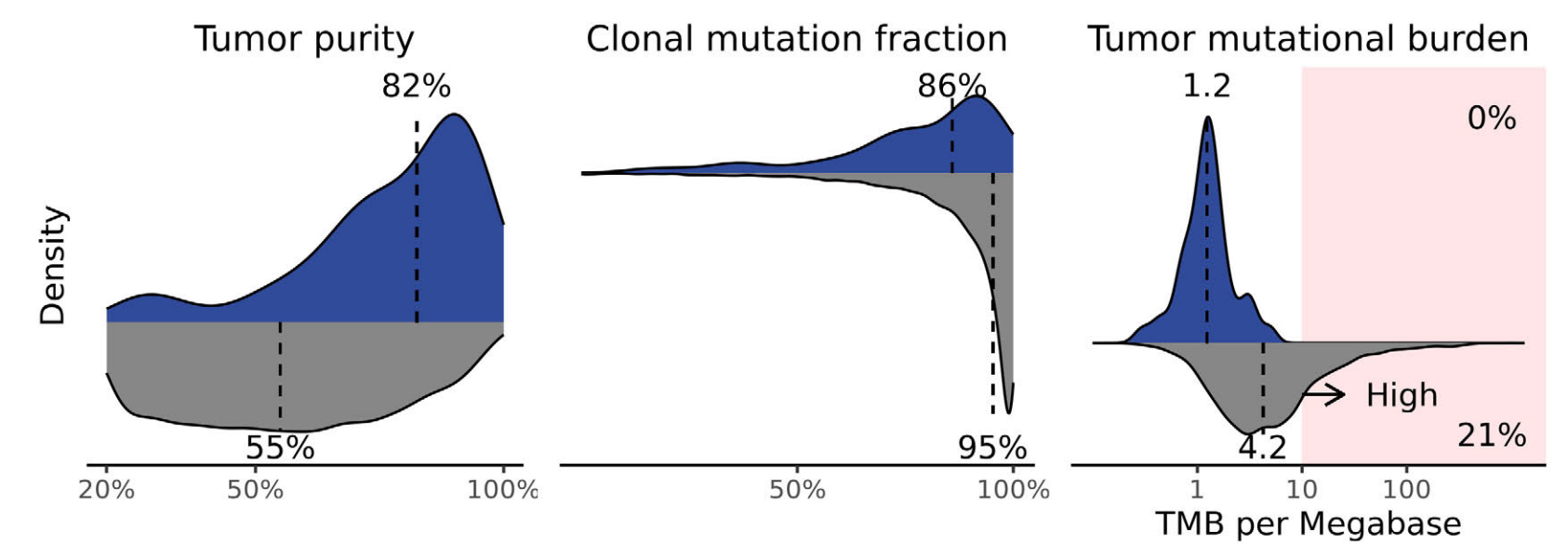
**Somatic drivers**: 43% (6+), 44% (6+); 57% (1-5), 1-5

**Oncogenes**: 14% None; 33% 3+, 32% 3+; 53% 1-2, 50% 1-2

**TSGs**: 5% None; 64% 3+, 61% 3+; 31% 1-2, 33% 1-2

| Gene | Type | Bile duct (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CDKN2A | TSG | 52 | 25 | ▲ |
| TP53 | TSG | 37 | 55 | ▼ |
| KRAS | ONC | 27 | 15 | ▲ |
| PBRM1 | TSG | 20 | 3.2 | ▲ |
| BAP1 | TSG | 18 | 2.7 | ▲ |
| SMAD4 | TSG | 17 | 8 | ▲ |
| ARID1A | TSG | 16 | 6 | ▲ |
| IDH1 | ONC | 11 | 1.3 | ▲ |
| FGFR2 | TSG | 9.9 | 1.2 | ▲ |
| EPHA2 | TSG | 8.9 | 0.6 | ▲ |
| ERBB2 | TSG | 8.9 | 5.7 | |
| TGFBR2 | TSG | 8.9 | 2.7 | ▲ |
| MDM2 | ONC | 7.9 | 3.3 | |
| BRAF | ONC | 5.9 | 6.2 | |
| MACROD2 | TSG | 5.9 | 1.5 | ▲ |
| MYC | ONC | 5.9 | 5.7 | |
| NF1 | TSG | 5.9 | 5 | |
| PIK3CA | ONC | 5.9 | 13 | ▼ |
| ATM | TSG | 5 | 2.9 | |
| ELF3 | TSG | 5 | 1.3 | ▲ |
| FGFR2_BICC1 | ONC | 5 | 0.1 | ▲ |
| FHIT | TSG | 5 | 4.3 | |
| KMT2C | TSG | 5 | 3.7 | |
| MAP2K4 | TSG | 5 | 3.9 | |
| MLH1 | TSG | 5 | 0.6 | ▲ |
| RASA1 | TSG | 5 | 1.3 | ▲ |
| TERT | ONC | 5 | 13 | ▼ |
| BRCA2 | TSG | 4 | 1.2 | ▲ |
| FGF3 | ONC | 4 | 5.2 | |

101 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events

**Actionable**: 7% None, 18% None; 33% 3+, 26% 3+; 60% 1-2, 56% 1-2

**Best treatment option**: 7% None/18% None; 13% Oth/14% Oth; Exp 5%; 43% Off/28% Off; 37% FDA/36% FDA

| Gene/Event | Bile duct (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 50 | 24 | ▲ |
| KRAS | 27 | 14 | ▲ |
| IDH1 | 11 | 1 | ▲ |
| ERBB2 | 8.9 | 5.6 | |
| FGFR2 | 8.9 | 1.1 | ▲ |
| HR deficiency | 8.9 | 5.8 | |
| TMB High | 7.9 | 21 | ▼ |
| MSI High | 6.9 | 3.1 | |
| BRAF | 5.9 | 5.9 | |
| BRCA2 | 5.9 | 2.4 | |
| PIK3CA | 5.9 | 13 | ▼ |
| ATM | 5 | 3.5 | |
| FGFR2 - BICC1 fusion | 5 | 0.1 | ▲ |
| CCND1 | 5 | 5.3 | |
| CHEK2 | 3 | 3 | |
| NF2 | 3 | 1.6 | |
| PTEN | 3 | 13 | ▼ |
| BRCA1 | 2 | 1.3 | |
| CDK4 | 2 | 2.7 | |
| CTNNB1 | 2 | 2.7 | |
| FGFR1 | 2 | 3.8 | |
| FGFR2 - TBC1D4 fusion | 2 | 0 | ▲ |
| IDH2 | 2 | 0.1 | ▲ |
| Rest FDA | 6.9 | | |
| Rest Repurpose | 8.9 | | |
| Rest Experimental | 1 | | |
| Rest Other | 6.9 | | |

94 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events / Summary / Top potential germline drivers

**Germline drivers**: 79% None, 84% None; 21% 1+, 16% 1+

| Gene | Type | Bile duct (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 4 | 3.2 | |
| MSH2 | TSG | 4 | 1 | ▲ |
| MUTYH | TSG | 3 | 1.9 | |
| BAP1 | TSG | 2 | 0.1 | ▲ |
| BRCA1 | TSG | 2 | 1.1 | |
| BRCA2 | TSG | 2 | 1.5 | |
| MLH1 | TSG | 2 | 0.2 | ▲ |
| BARD1 | TSG | 1 | 0.1 | ▲ |
| MITF | ONC | 1 | 0.7 | |

20 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy

| Test | FDA | Drug Repurposing | Exp/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 37 | 43 | 8 | 7 | 6 |
| Comprehensive 521 gene panel | 24 | 46 | 8 | 10 | 13 |
| Targeted 50 gene panel | 22 | 39 | 9 | 29 | |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.45 | 0.94 | 0.3 | 0.81 | 2.5 |
| Comprehensive 521 gene panel | 0.31 | 0.74 | 0.23 | 0.59 | 1.9 |
| Targeted 50 gene panel | 0.22 | 0.53 | 0.49 | | 1.3 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**: Fusion 14
**Drug Repurposing**: HRD 9; HMZ Disruption 6; Partial CN Loss 5
**Experimental/Other Guidelines**: Partial CN Loss 7
**Other**: Partial CN Loss 15; Full CN Loss 3; Small Variant 2; HMZ Disruption 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**: Fusion 14; TMB High 8; Small Variant 1
**Drug Repurposing**: Small Variant 18; HRD 9; HMZ Disruption 6; Partial CN Loss 5; Full CN Loss 1
**Experimental/Other Guidelines**: Full CN Gain 9; Partial CN Loss 7; Full CN Loss 6; Small Variant 1
**Other**: Partial CN Loss 15; Small Variant 12; Full CN Loss 3; HMZ Disruption 2; Splice Site 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Gastrointestinal Stromal Tumor

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 78 |
| RNASeq | 37 |
| Age, Sex | 58 |
| Biopsy site | 53 |
| Pretreatment | 50 |
| Treatment | 46 → |
| Response | 42 → |

### Patients with treatment and response data

**Post-biopsy treatment**

| | |
|---|---|
| Chemo | 0 |
| Multiple | 0 |
| Targeted | 45 |
| Hormonal | 0 |
| Immuno | 1 |
| Radio | 2 |
| Other | 0 |
| None or NA | 0 |

**Responders**

| | |
|---|---|
| Chemo | 0 |
| Multiple | 0 |
| Targeted | 17 (38%) |
| Hormonal | 0 |
| Immuno | 0 |
| Radio | 1 (50%) |
| Other | 0 |
| None or NA | 0 |

## Tumor Characteristics

Legend: GIST (blue), Pan-Cancer (grey)

| | GIST | Pan-Cancer |
|---|---|---|
| TMB High | 0% | 21% |
| MSI High | 0% | 2% |
| WGD | 26% | 56% |
| Diploid Proportion | 51% | 34% |
| GIE HLA LOH | 17% | 19% |
| GIE Overall | 17% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
GIST 82%, Pan-Cancer 55%

### Clonal mutation fraction
GIST 86%, Pan-Cancer 95%

### Tumor mutational burden
1.2, High 4.2 — GIST 0%, 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| GIST | 3,255 | 292 | 46 | 18 |

Number of variants vs Quantile

### Telomere Length
0.73 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
4 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.05 / 0.15 — Instable, GIST 0%, 2%
MS indels per megabase

### Mean genome ploidy
1.9 / 2.6

### Aneuploidy Score
9 / 16

### % Copy number alteration
34% / 54%

### % Genome LOH
28% / 24%

## Processes Underlying Mutations

- DNA damage repair: 14%
- Ageing: 13%
- Chemical exposure: 11%
- APOBEC: 3%
- Tobacco: 2%
- UV light: 1%
- Unknown: 56%

## GIST
78 Patients

## Pan-Cancer
6790 Patients

Gastrointestinal

Made with bioRender

## Copy Number Alteration Profile

Genes labeled: BCL2, NF1, MGA, MAX, RB1, DEPDC5, DMD, KDM6A, AGBL4, ABID1A, LINC00290, CDKN2C, LRP1B, CCSER1, FBXW7, TERT, FBXL17, JAK2, CDKN2A, PTEN, LINC00301, MDM2, CDK4

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers**

| | GIST (%) | Pan-Cancer (%) |
|---|---|---|
| 6+ | 5% | 44% |
| 1-5 | 90% | 54% |

**Oncogenes**

| | |
|---|---|
| 3+ | 12% / 18% |
| 1-2 | 87% / 50% |

**TSGs**

| | |
|---|---|
| 3+ | 12% / 61% |
| 1-2 | 54% / 33% |

| Gene | Type | GIST % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| KIT | ONC | 76 | 1.8 | ▲ |
| CDKN2A | TSG | 40 | 25 | |
| DMD | TSG | 35 | 3.5 | ▲ |
| RB1 | TSG | 23 | 11 | ▲ |
| MAX | TSG | 10 | 0.5 | ▲ |
| NF1 | TSG | 9 | 5 | |
| KIT_KIT | ONC | 7.7 | 0.1 | ▲ |
| LRP1B | TSG | 7.7 | 2.1 | ▲ |
| TP53 | TSG | 7.7 | 55 | ▼ |
| PTEN | TSG | 5.1 | 14 | ▼ |
| SETD2 | TSG | 5.1 | 2.1 | |
| ARID1A | TSG | 3.8 | 6 | |
| CDKN2C | TSG | 3.8 | 0.4 | ▲ |
| DEPDC5 | TSG | 3.8 | 0.4 | ▲ |
| BRAF | ONC | 2.6 | 6.2 | |
| CCSER1 | TSG | 2.6 | 1.1 | ▲ |
| GRIN2A | TSG | 2.6 | 0.5 | ▲ |
| LZTR1 | TSG | 2.6 | 0.3 | ▲ |
| MGA | TSG | 2.6 | 1.5 | |
| NTRK2 | ONC | 2.6 | 0.1 | ▲ |
| PDGFRA | TSG | 2.6 | 0.8 | ▲ |
| PIK3CA | ONC | 2.6 | 13 | ▼ |
| STK11 | TSG | 2.6 | 4.1 | |
| TERT | ONC | 2.6 | 13 | ▼ |
| AGBL4 | TSG | 1.3 | 0.1 | ▲ |
| ATM | TSG | 1.3 | 2.9 | |
| ATRX | TSG | 1.3 | 2.4 | |
| BCL2 | ONC | 1.3 | 0.1 | ▲ |
| CDK4 | ONC | 1.3 | 2 | |

### Top cancer drivers
73 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange), FUSION (light blue)

## Potentially Actionable Events

### # Events

**Actionable**

| | GIST | Pan-Cancer |
|---|---|---|
| None | 8% | 18% |
| 3+ | 9% | 26% |
| 1-2 | 83% | 56% |

**Best treatment option**

| | GIST | Pan-Cancer |
|---|---|---|
| None | 8% | 18% |
| Oth | 8% | 14% |
| Exp | 4% | 5% |
| Off | | 28% |
| FDA | 81% | 36% |

### Summary

| Gene | GIST % | Pan-Cancer % | Direction |
|---|---|---|---|
| KIT | 77 | 1.1 | ▲ |
| CDKN2A | 40 | 24 | |
| KIT - KIT fusion | 7.7 | 0.1 | ▲ |
| PTEN | 5.1 | 13 | ▼ |
| BRAF | 2.6 | 5.9 | |
| PDGFRA | 2.6 | 0.1 | ▲ |
| PIK3CA | 2.6 | 13 | ▼ |
| ATM | 1.3 | 3.5 | |
| BCL2 | 1.3 | 0.1 | ▲ |
| CDK4 | 1.3 | 1.9 | |
| CHEK2 | 1.3 | 3 | |
| CTNNB1 | 1.3 | 2.7 | |
| FGFR1 | 1.3 | 3.8 | |
| KMT2D | 1.3 | 2.9 | |
| RAD51C | 1.3 | 0.1 | ▲ |

### Top potential actionable events
72 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

**Germline drivers**

| | GIST | Pan-Cancer |
|---|---|---|
| None | 86% | 84% |
| 1+ | 14% | 16% |

### Summary

| Gene | Type | GIST % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| SDHA | TSG | 3.8 | 0.5 | ▲ |
| MSH2 | TSG | 2.6 | 1 | ▲ |
| NF1 | TSG | 2.6 | 0.2 | ▲ |
| ATM | TSG | 1.3 | 1 | |
| CHEK2 | TSG | 1.3 | 3.2 | |
| EPCAM | TSG | 1.3 | 0.1 | ▲ |
| KIT | ONC | 1.3 | 0 | ▲ |
| RAD51C | TSG | 1.3 | 0.1 | ▲ |
| SDHB | TSG | 1.3 | 0.1 | ▲ |

### Top potential germline drivers
11 Patients

Legend: STRUCTURAL_VARIANT (blue), SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Other | None |
|---|---|---|---|---|
| WGS | 63 | 3 | 6 | 6 |
| Comprehensive 521 gene panel | 61 | 3 | 3 | 11 |
| Targeted 50 gene panel | 61 | 3 | | 12 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Other | Total |
|---|---|---|---|---|
| WGS | 0.88 | 0.62 | 0.58 | 2.2 |
| Comprehensive 521 gene panel | 0.81 | 0.62 | 0.37 | 1.8 |
| Targeted 50 gene panel | 0.81 | 0.54 | 0.36 | 1.7 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Fusion: 6

**Drug Repurposing**

**Experimental/Other Guidelines**
- Partial CN Loss: 4

**Other**
- Partial CN Loss: 12
- Full CN Loss: 2
- HMZ Disruption: 1
- Partial CN Gain: 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- Fusion: 6

**Drug Repurposing**
- Small Variant: 6

**Experimental/Other Guidelines**
- Partial CN Loss: 4
- Full CN Gain: 1

**Other**
- Partial CN Loss: 12
- Full CN Loss: 2
- Small Variant: 1
- HMZ Disruption: 1
- Partial CN Gain: 1

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the % of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
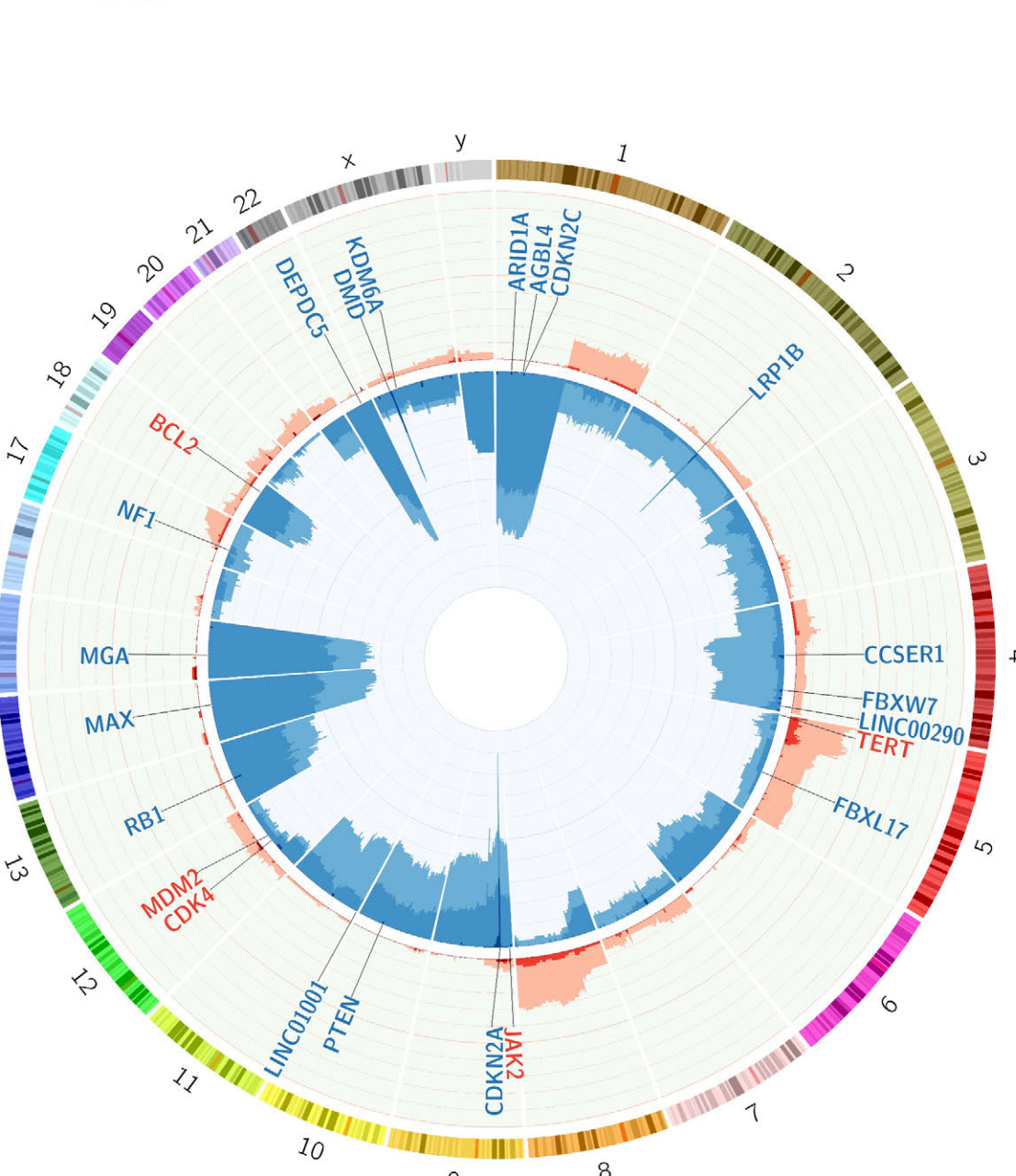Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

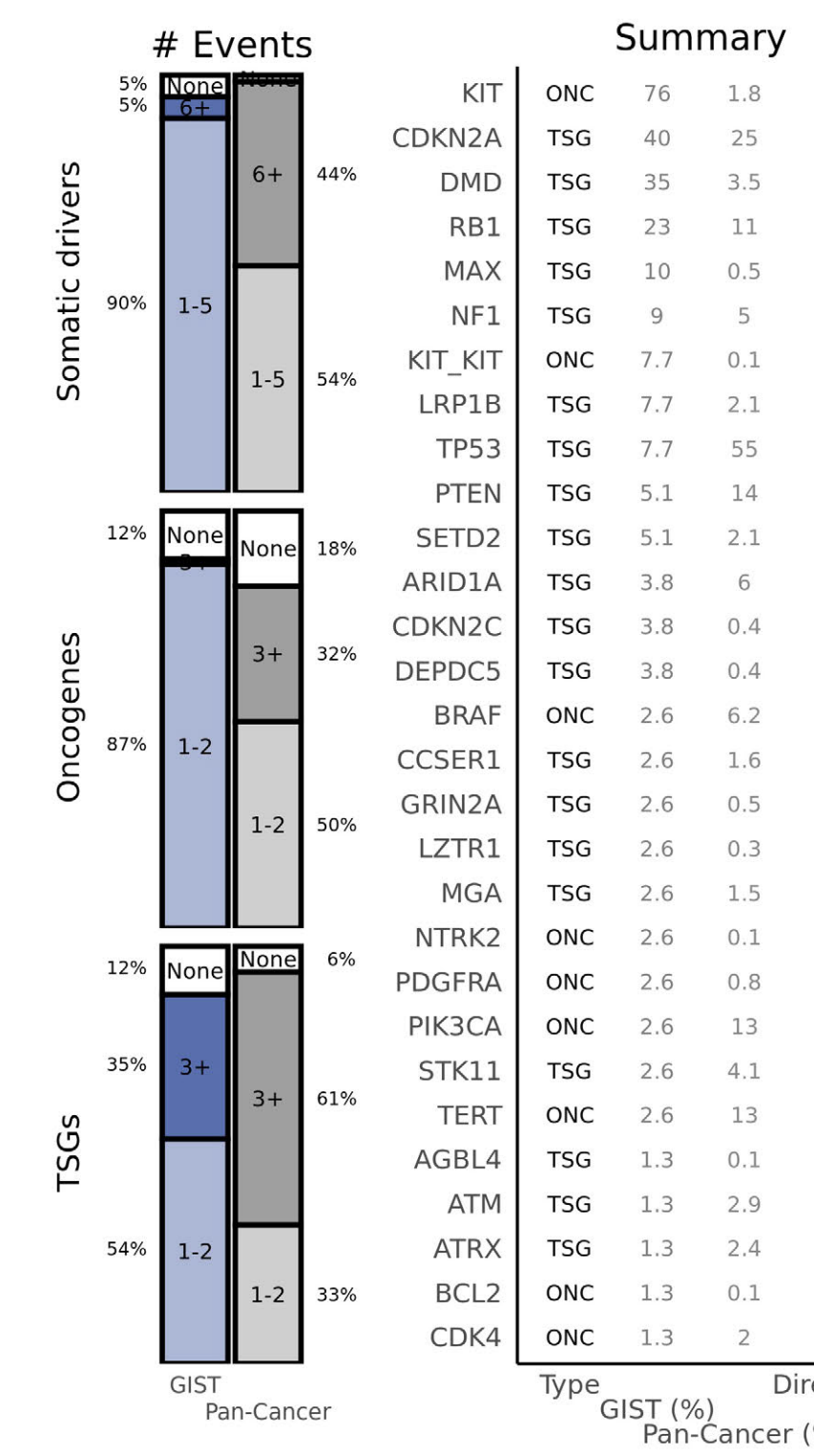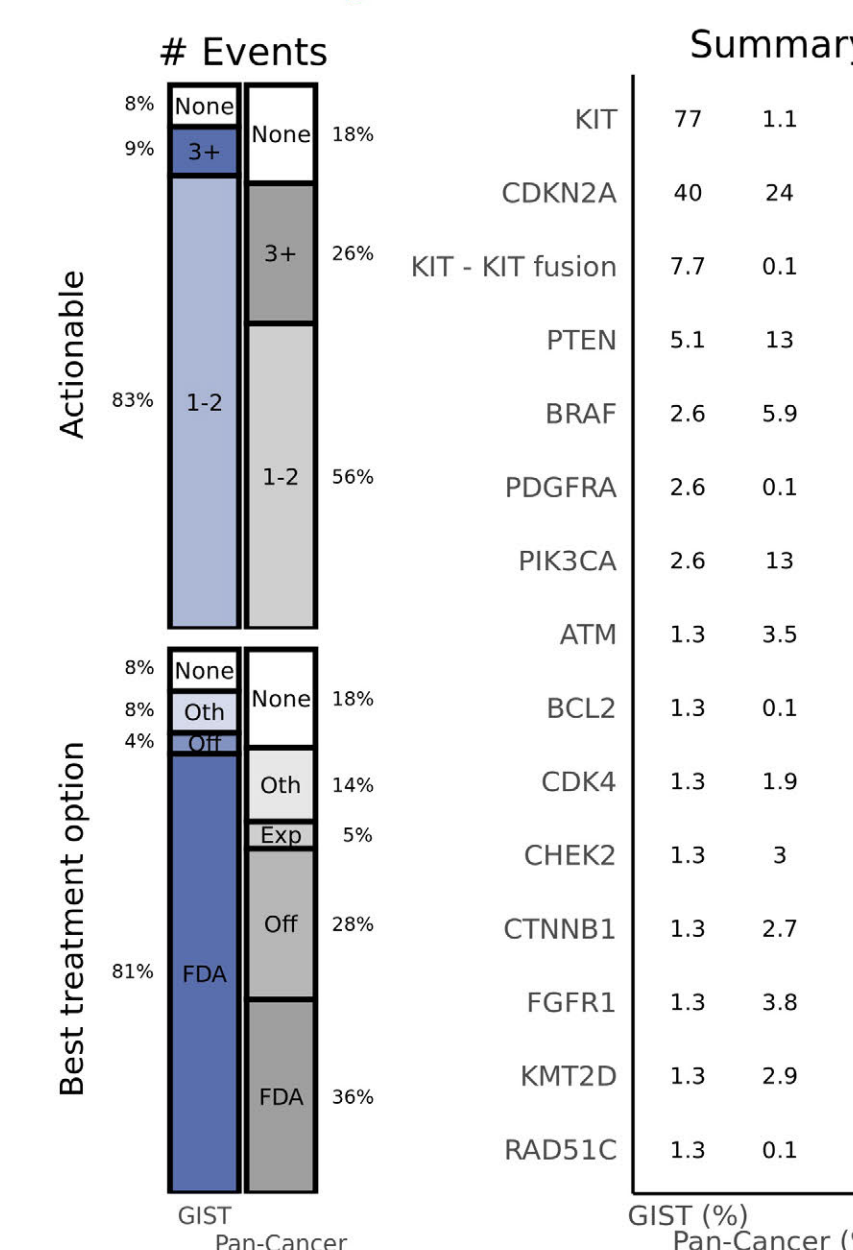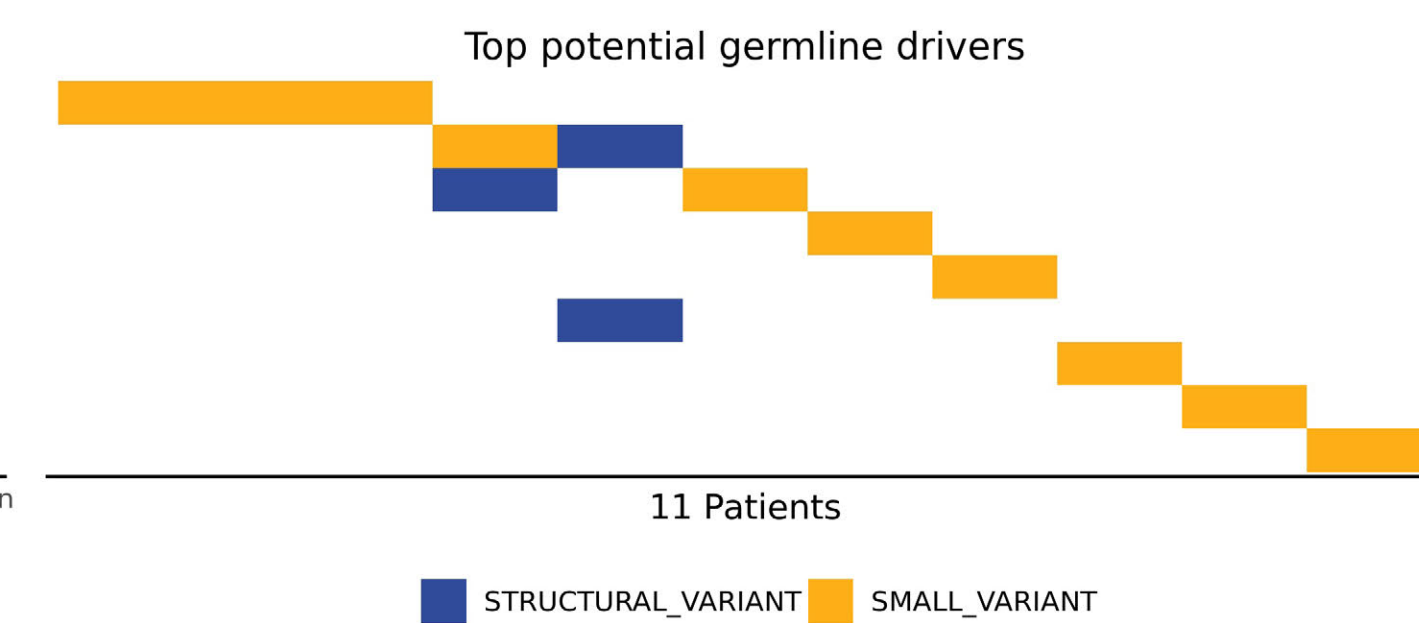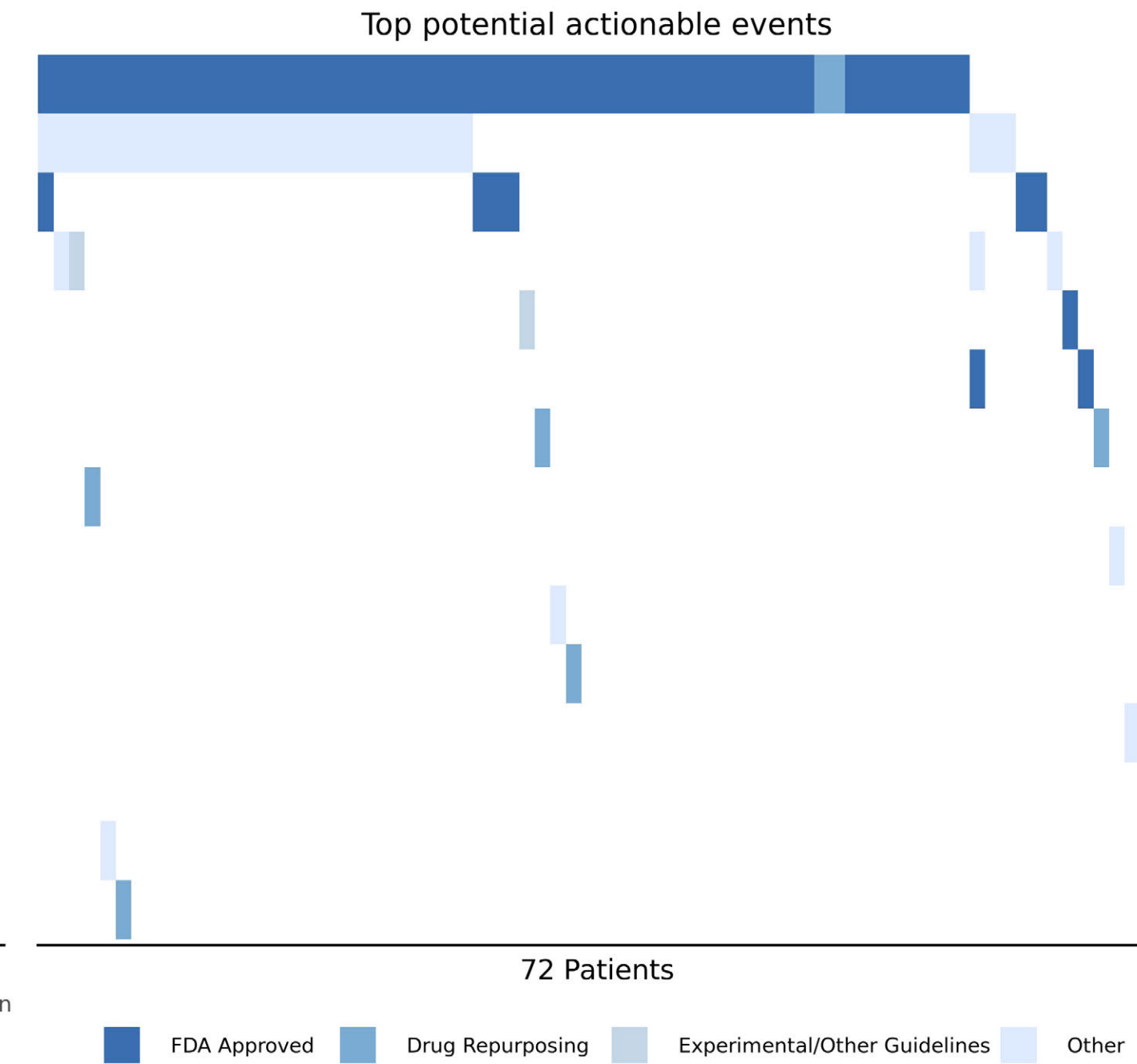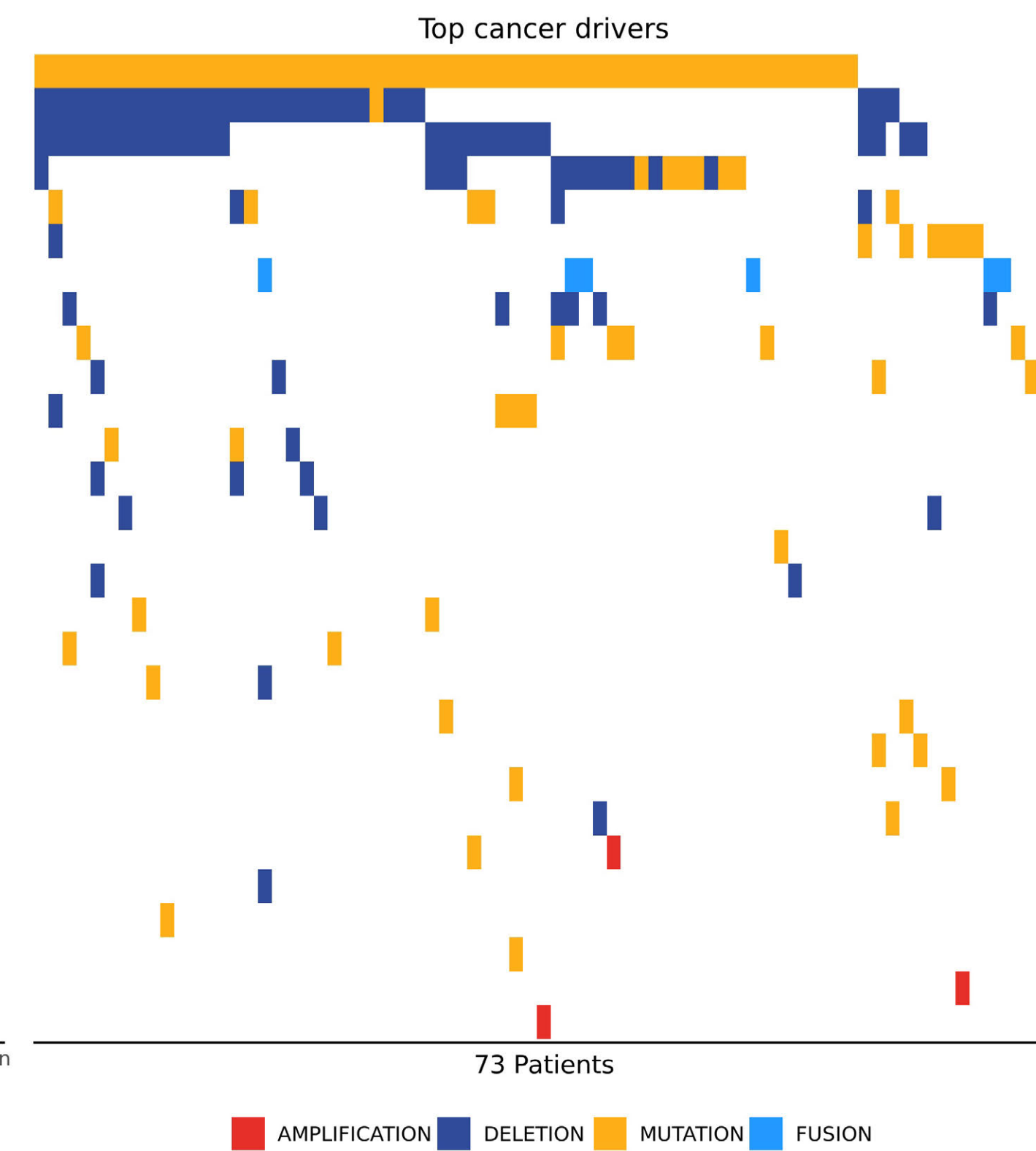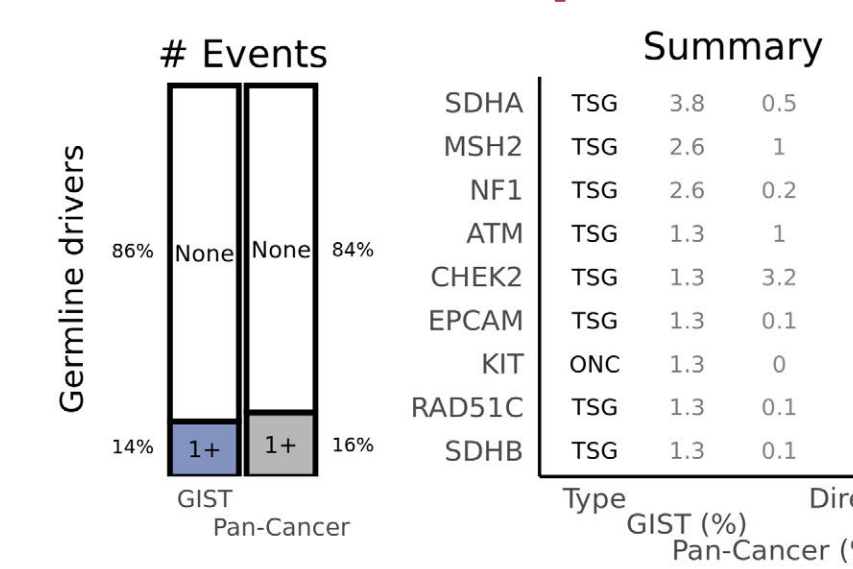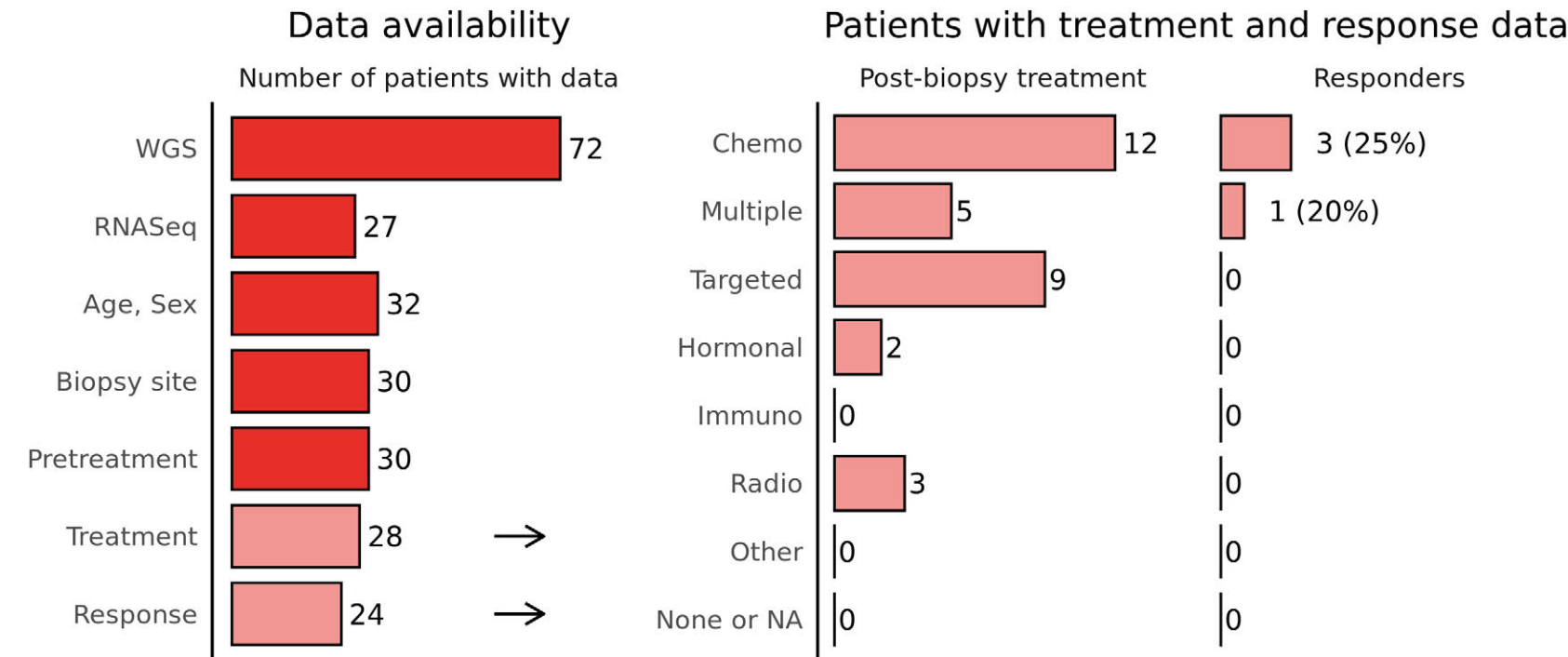Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: GIST
DOIDs included: 9253
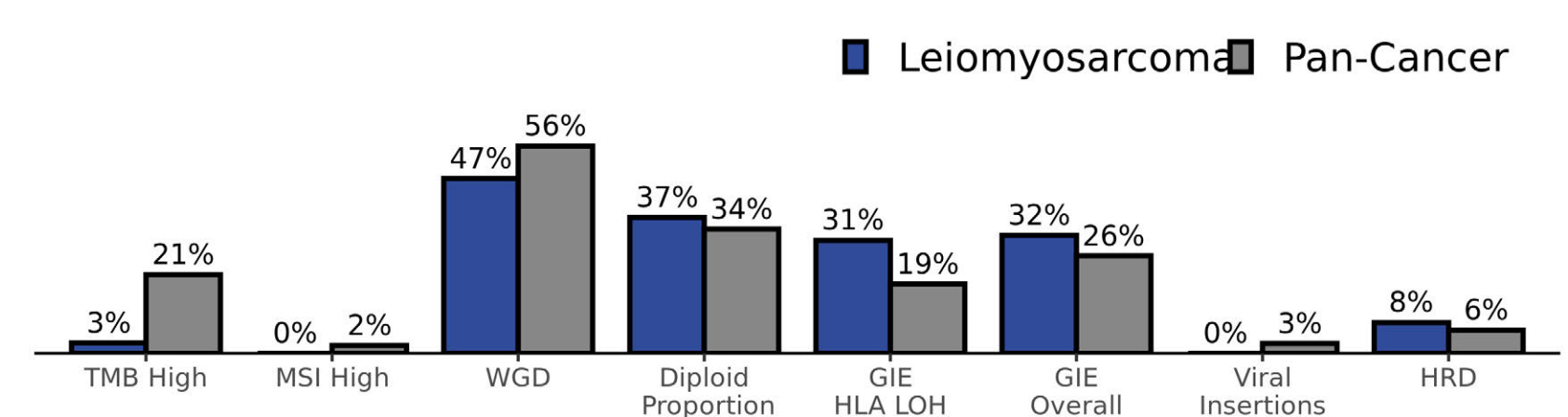Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High captured by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with min ring copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Disruptions, Viral inserts, HLA type assumed not captured by panels.
** See documentation for further details on the WGS vs Panel coverage study.

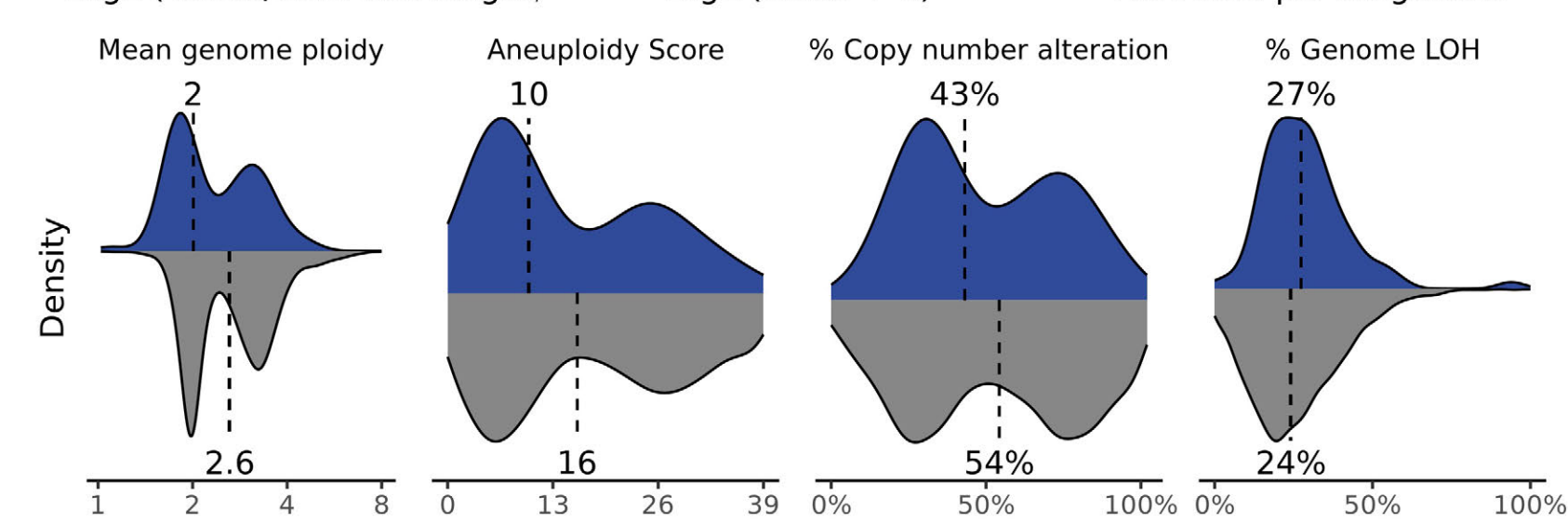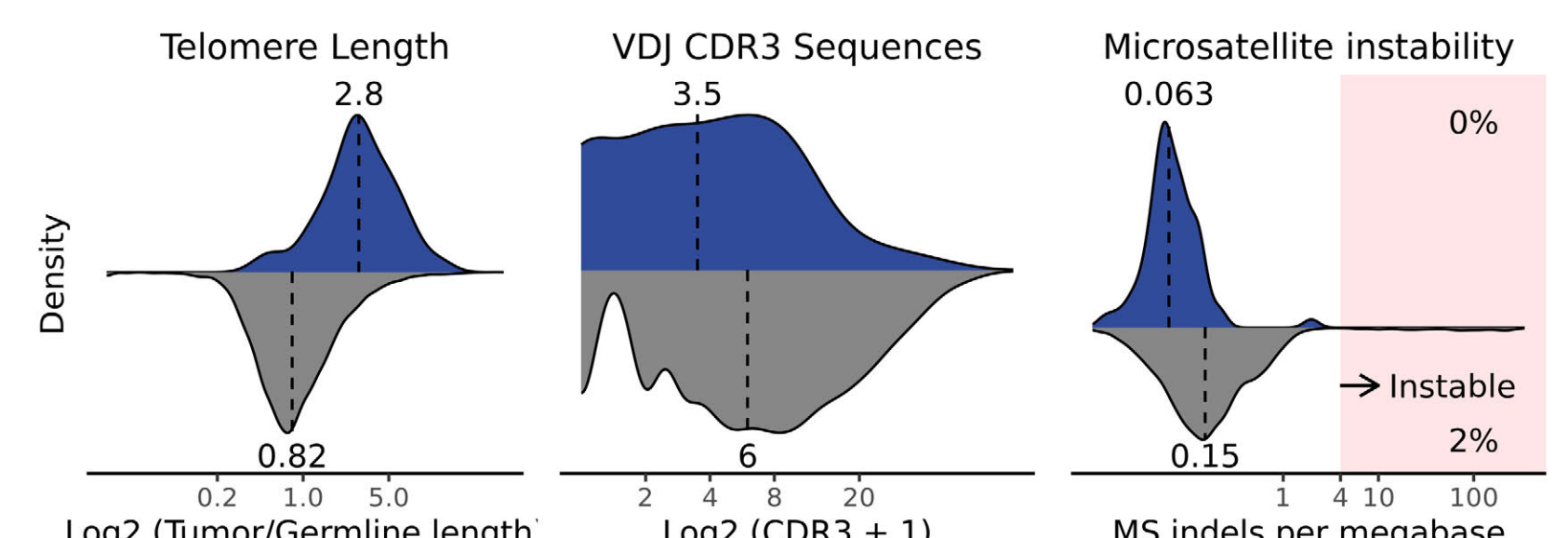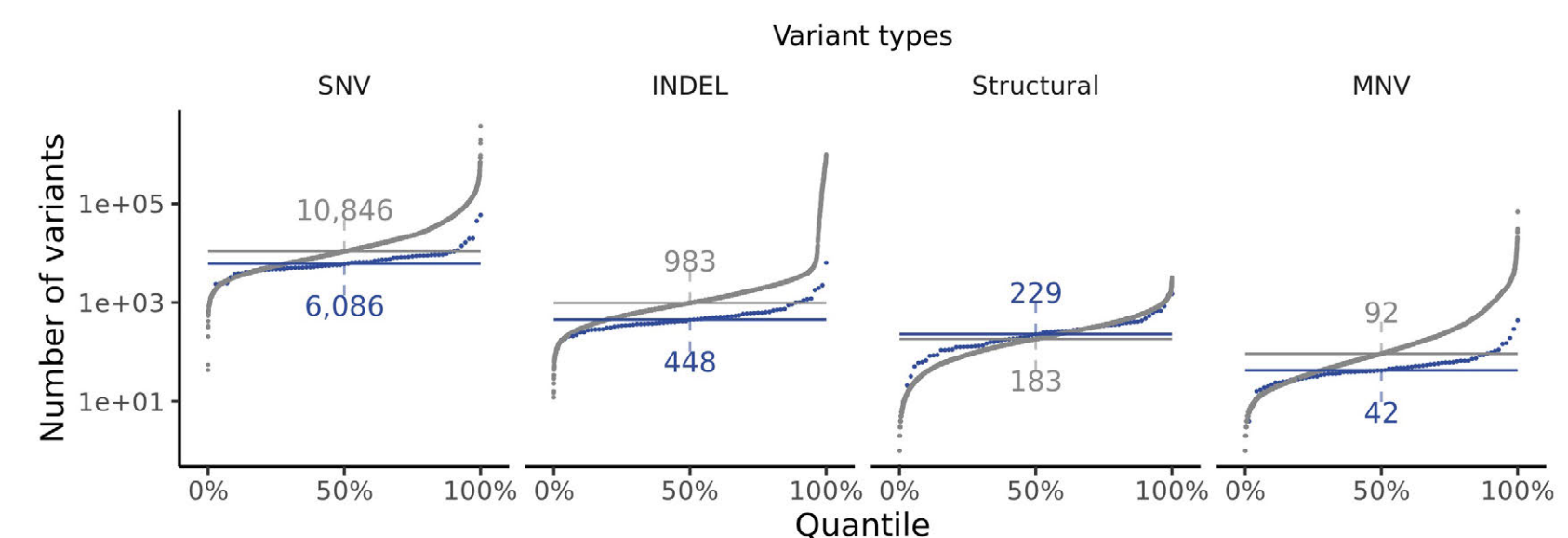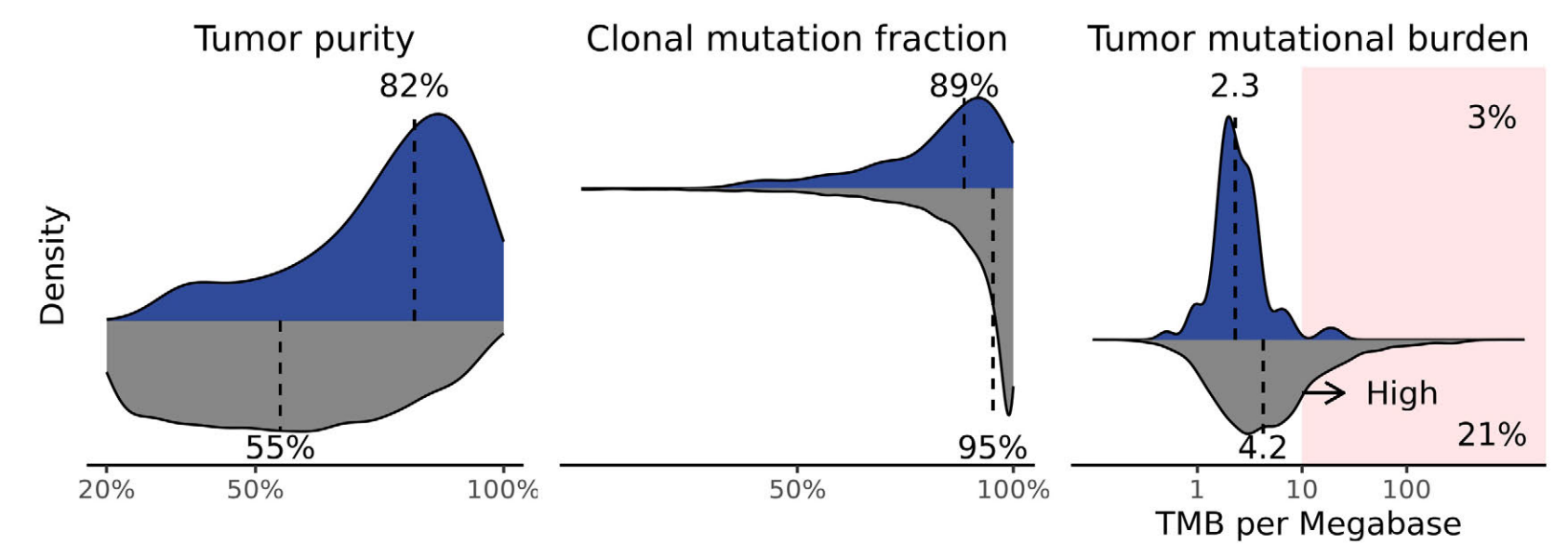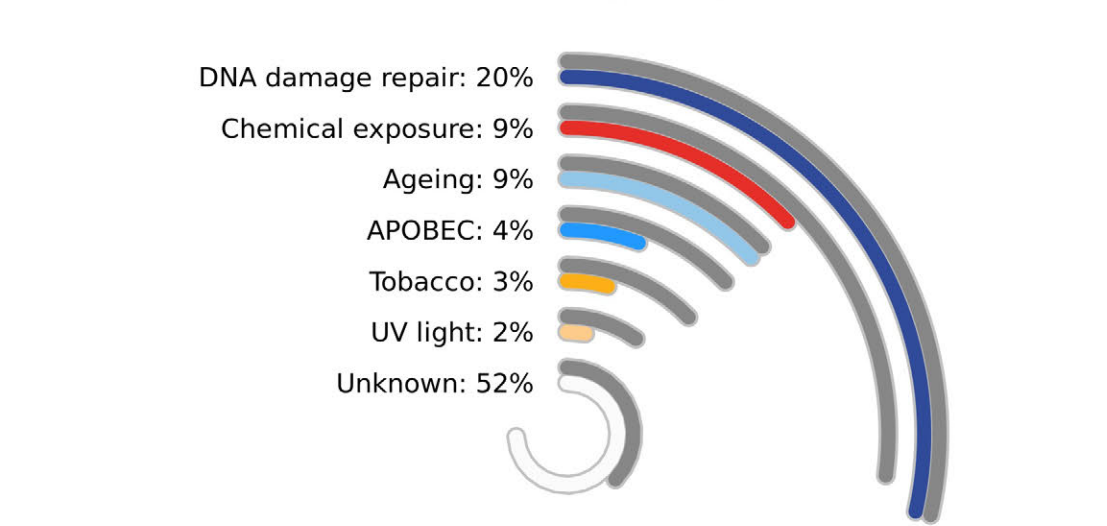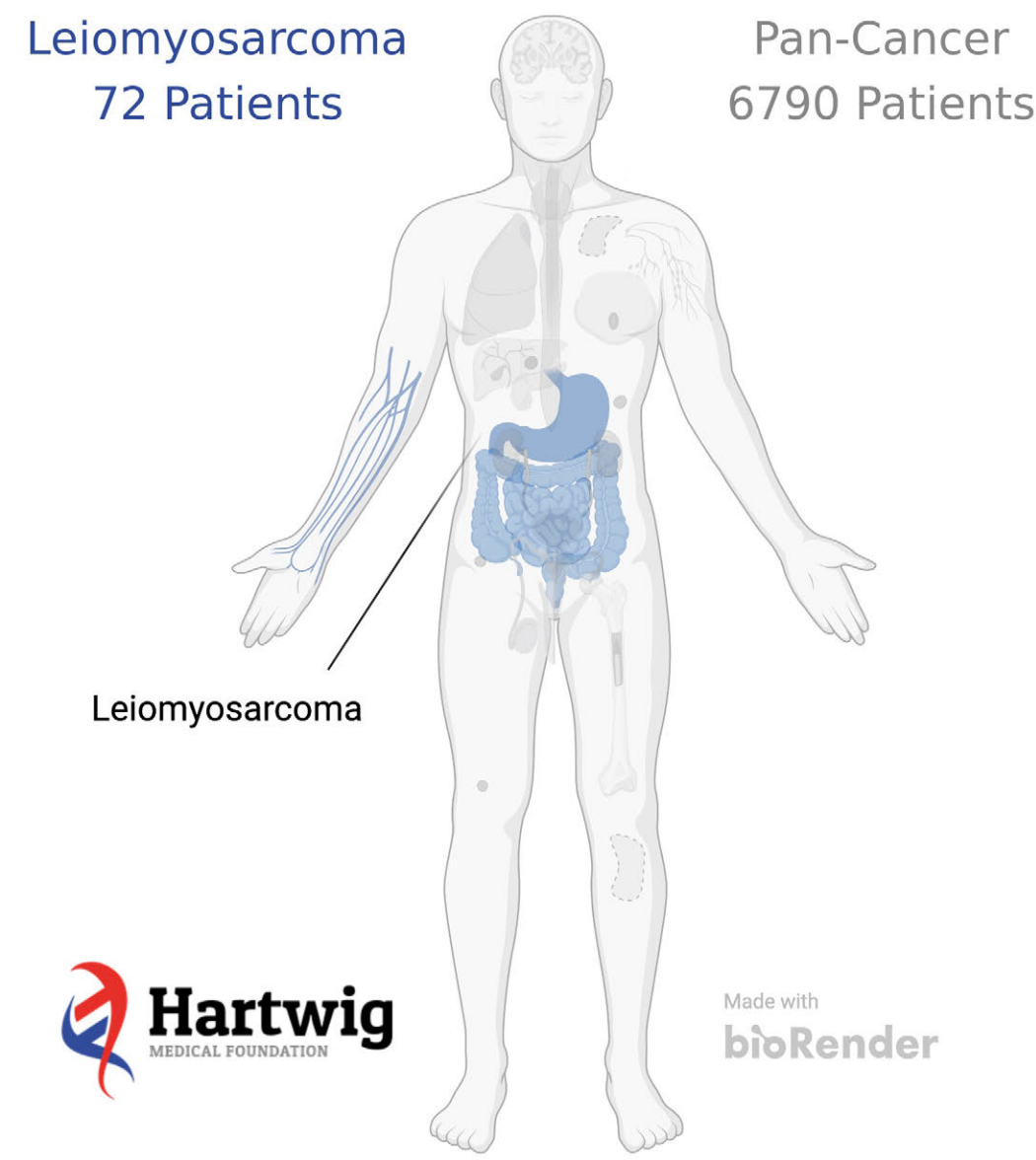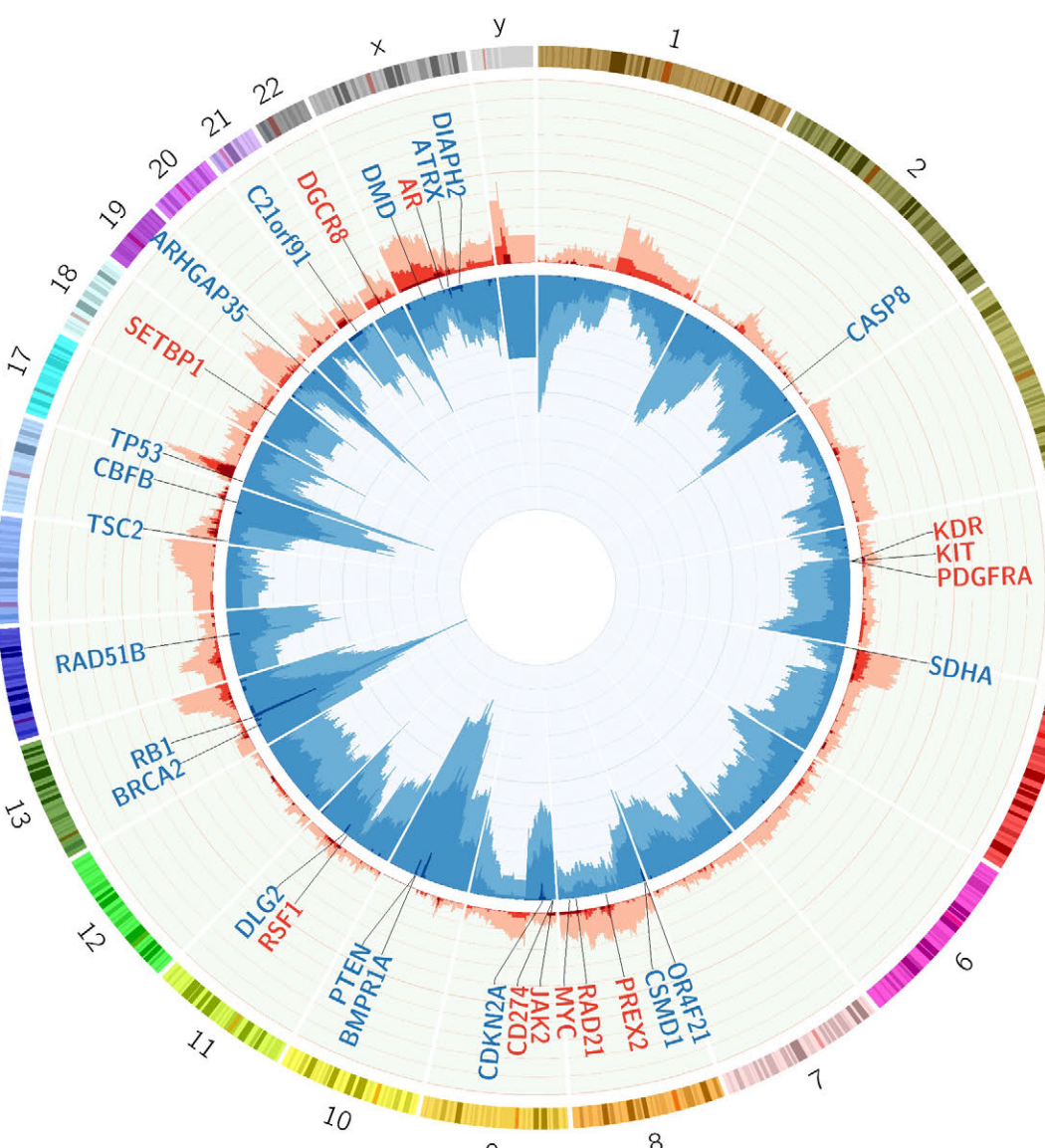# The Genomic And Actionability Landscape Of Leiomyosarcoma

## Cohort Metadata

### Data availability

**Number of patients with data**



### Patients with treatment and response data

Post-biopsy treatment — Responders



## Tumor Characteristics

■ Leiomyosarcoma ■ Pan-Cancer



## Mutational Landscape

### Tumor purity / Clonal mutation fraction / Tumor mutational burden



### Variant types

SNV / INDEL / Structural / MNV



### Telomere Length / VDJ CDR3 Sequences / Microsatellite instability



### Mean genome ploidy / Aneuploidy Score / % Copy number alteration / % Genome LOH



## Processes Underlying Mutations



- DNA damage repair: 20%
- Chemical exposure: 9%
- Ageing: 9%
- APOBEC: 4%
- Tobacco: 3%
- UV light: 2%
- Unknown: 52%

**Leiomyosarcoma 72 Patients**
**Pan-Cancer 6790 Patients**

Leiomyosarcoma



## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers



70 Patients

■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events



28 Patients

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events / Summary / Top potential germline drivers



11 Patients

■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing ■ Other ■ None

### Highest evidence level treatment option identified by test strategy



# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy



Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS



Number of Missed Events

### Top missed events by Targeted Panel vs WGS



Number of Missed Events

# The Genomic And Actionability Landscape Of Liposarcoma

## Cohort Metadata

### Data availability
**Number of patients with data**

- WGS: 50
- RNASeq: 7
- Age, Sex: 10
- Biopsy site: 10
- Pretreatment: 10
- Treatment: 10
- Response: 10

### Patients with treatment and response data
**Post-biopsy treatment** / **Responders**

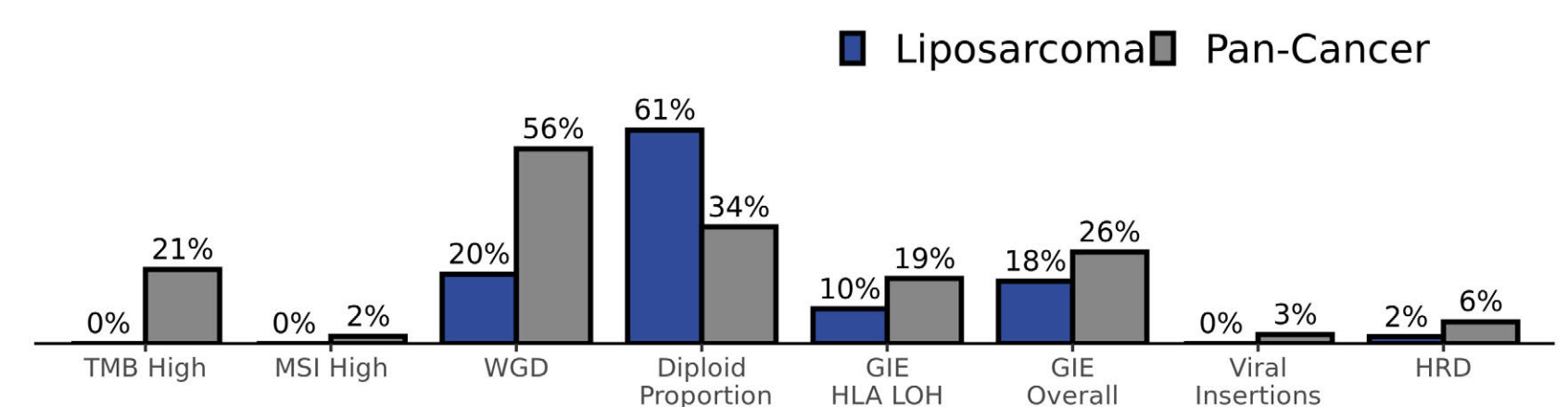- Chemo: 1 / 0
- Multiple: 8 / 2 (25%)
- Targeted: 0 / 0
- Hormonal: 0 / 0
- Immuno: 0 / 0
- Radio: 2 / 0
- Other: 1 / 0
- None or NA: 0 / 0

## Processes Underlying Mutations

- Ageing: 17%
- DNA damage repair: 11%
- Chemical exposure: 9%
- APOBEC: 8%
- UV light: 2%
- Tobacco: 1%
- Unknown: 52%

## Tumor Characteristics

**Liposarcoma** / **Pan-Cancer**

- TMB High: 0% / 21%
- MSI High: 0% / 2%
- WGD: 20% / 56%
- Diploid Proportion: 61% / 34%
- GIE HLA LOH: 10% / 19%
- GIE Overall: 18% / 26%
- Viral Insertions: 0% / 3%
- HRD: 2% / 6%

Liposarcoma 50 Patients
Pan-Cancer 6790 Patients

## Mutational Landscape

### Tumor purity
72% / 55%

### Clonal mutation fraction
90% / 95%

### Tumor mutational burden
1.4 / 4.2 — High 0% / 21%
TMB per Megabase

### Variant types
- SNV: 10,846 / 3,560
- INDEL: 983 / 342
- Structural: 647 / 183
- MNV: 92 / 34

Number of variants — Quantile

### Telomere Length
1.4 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
5 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.041 / 0.15 — Instable 0% / 2%
MS indels per megabase

### Mean genome ploidy
2 / 2.6

### Aneuploidy Score
4 / 16

### % Copy number alteration
25% / 54%

### % Genome LOH
15% / 24%

## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events

**Somatic drivers**: 34% 6+ / 44% 6+ ; 66% 1-5 / 54% 1-5
**Oncogenes**: 6% None / 18% None ; 60% 3+ / 32% 3+ ; 34% 1-2 / 50% 1-2
**TSGs**: 40% None / 61% 3+ ; 16% 3+ ; 44% 1-2 / 33% 1-2

### Summary

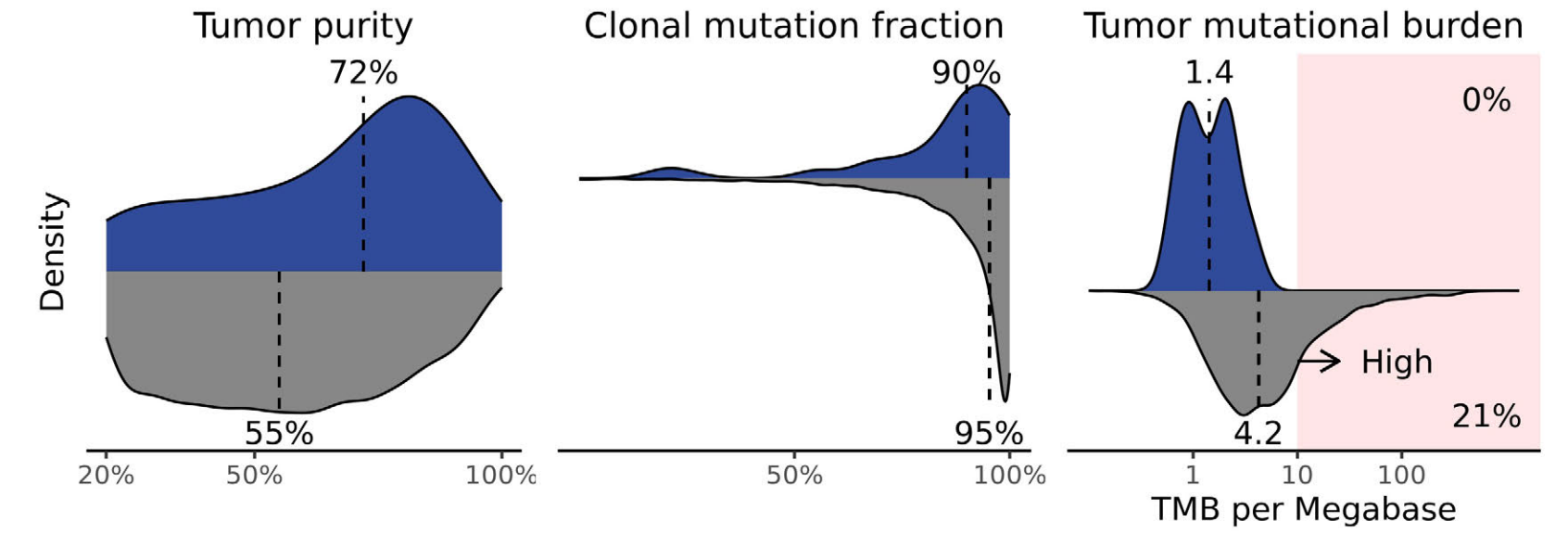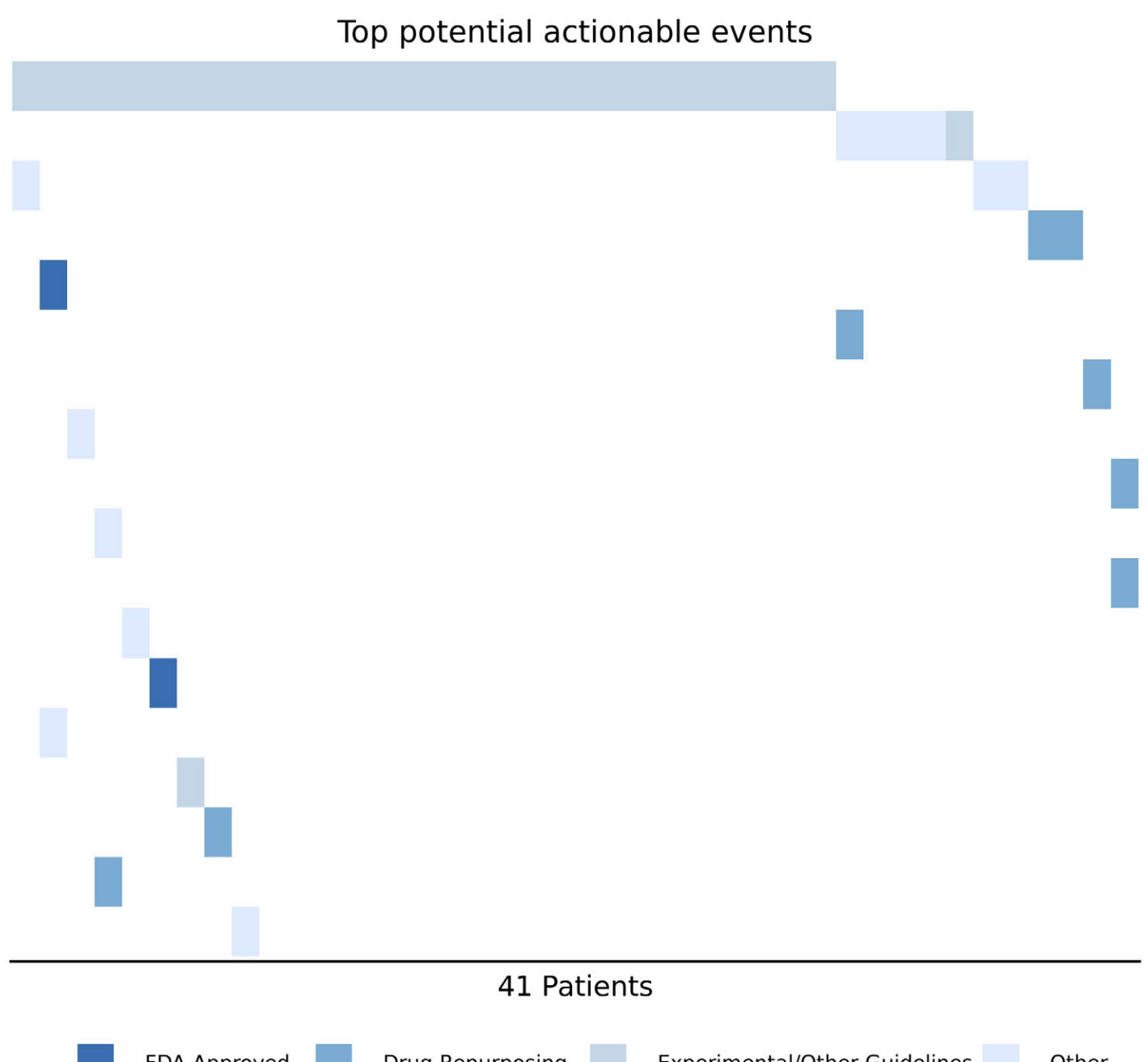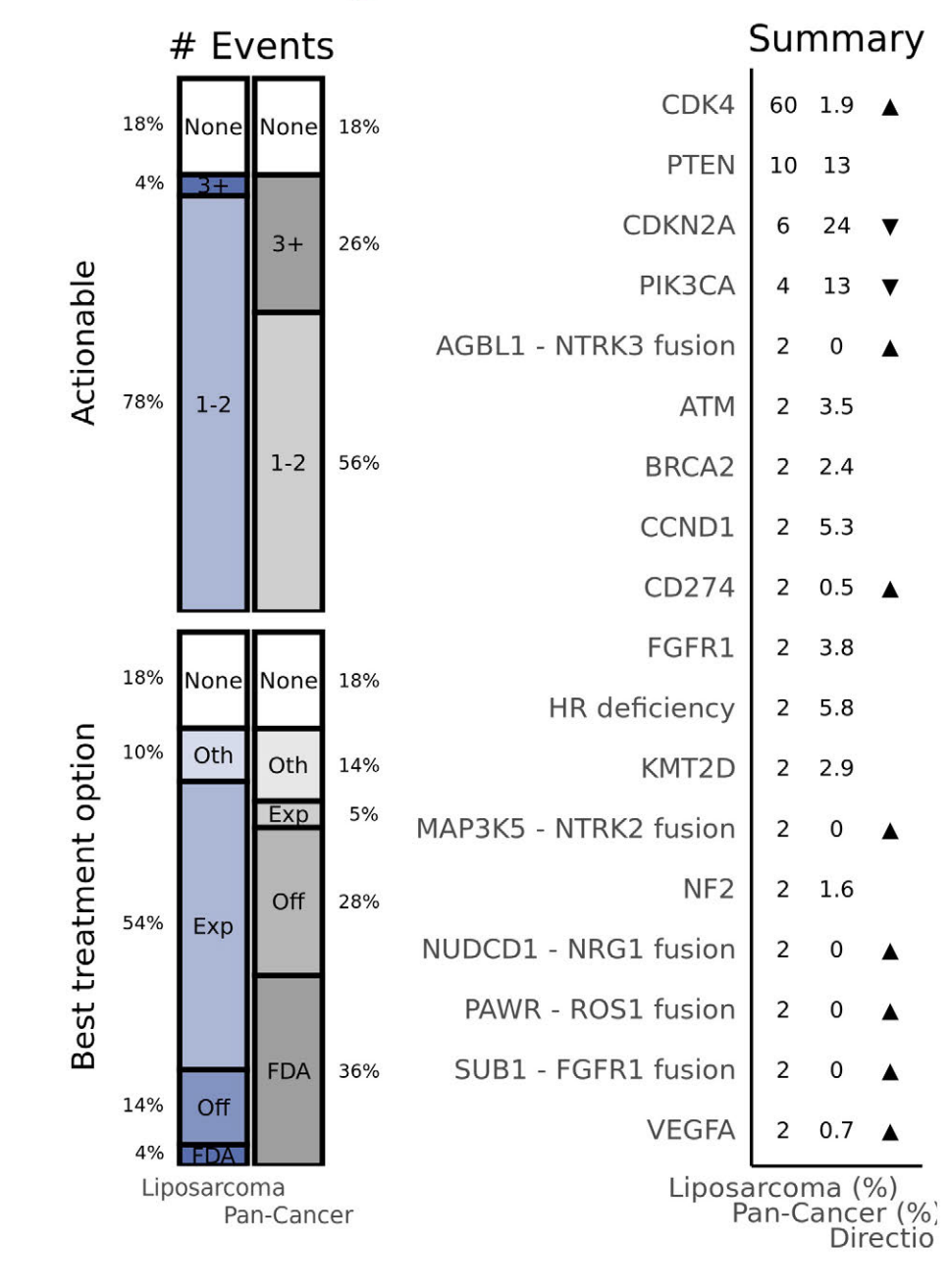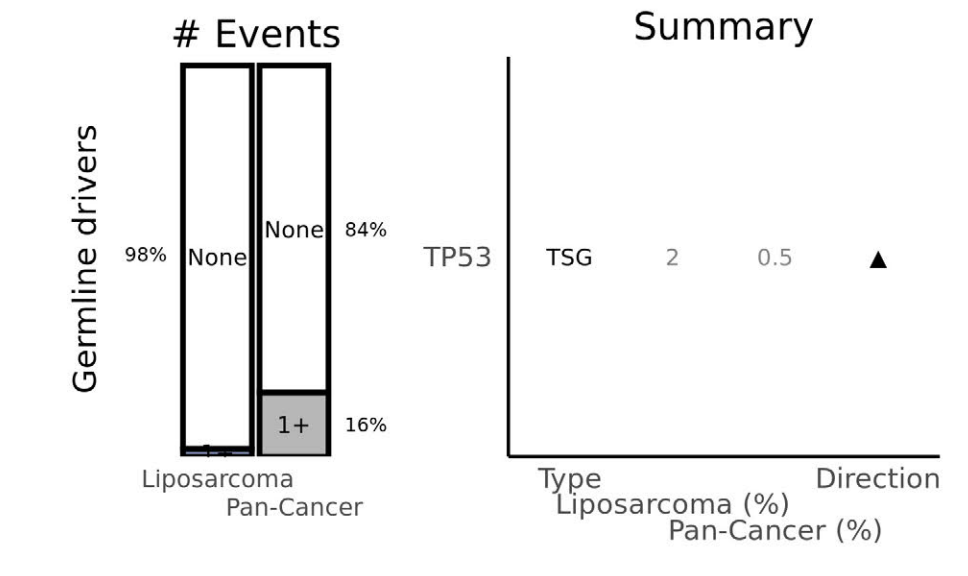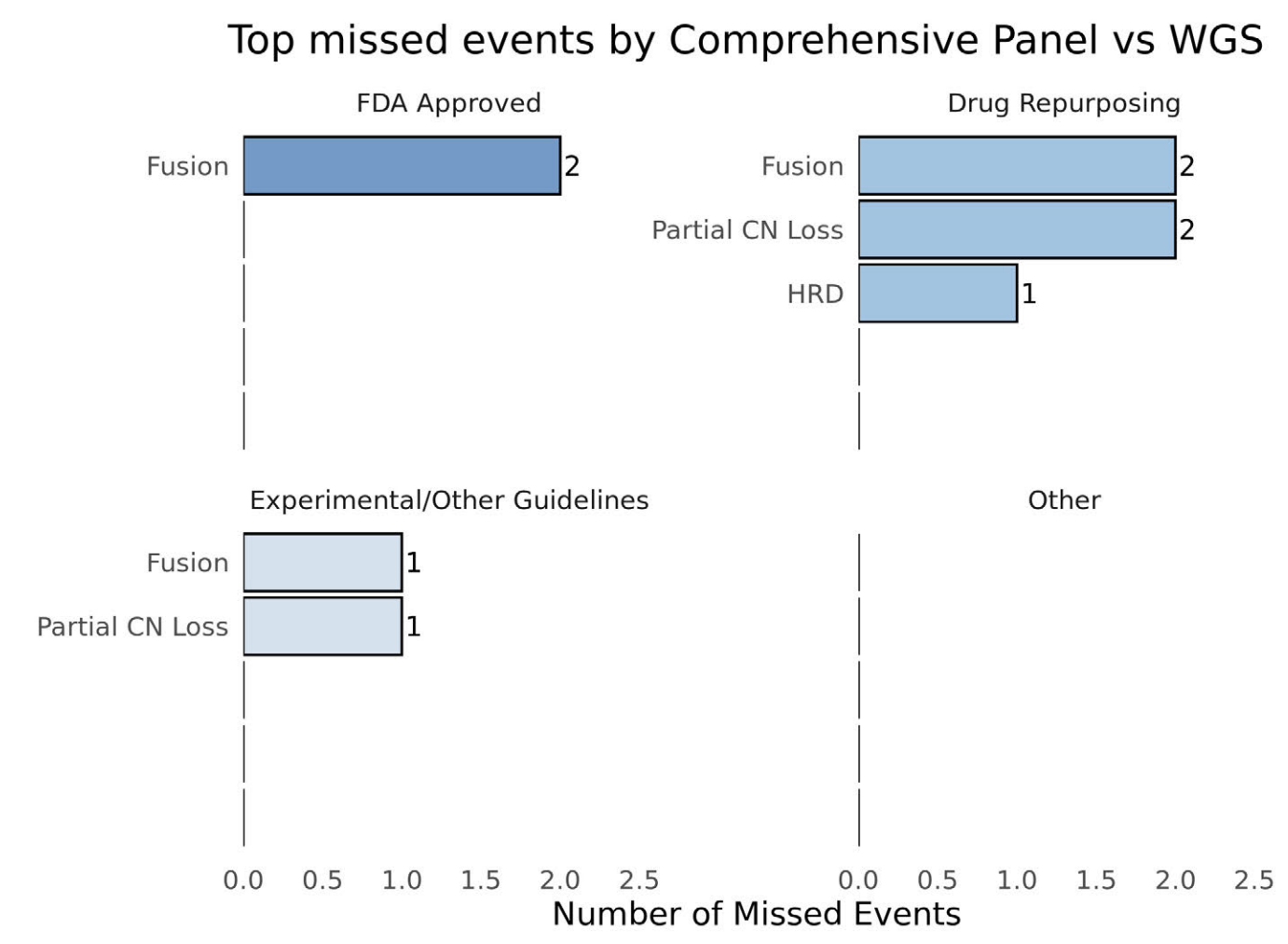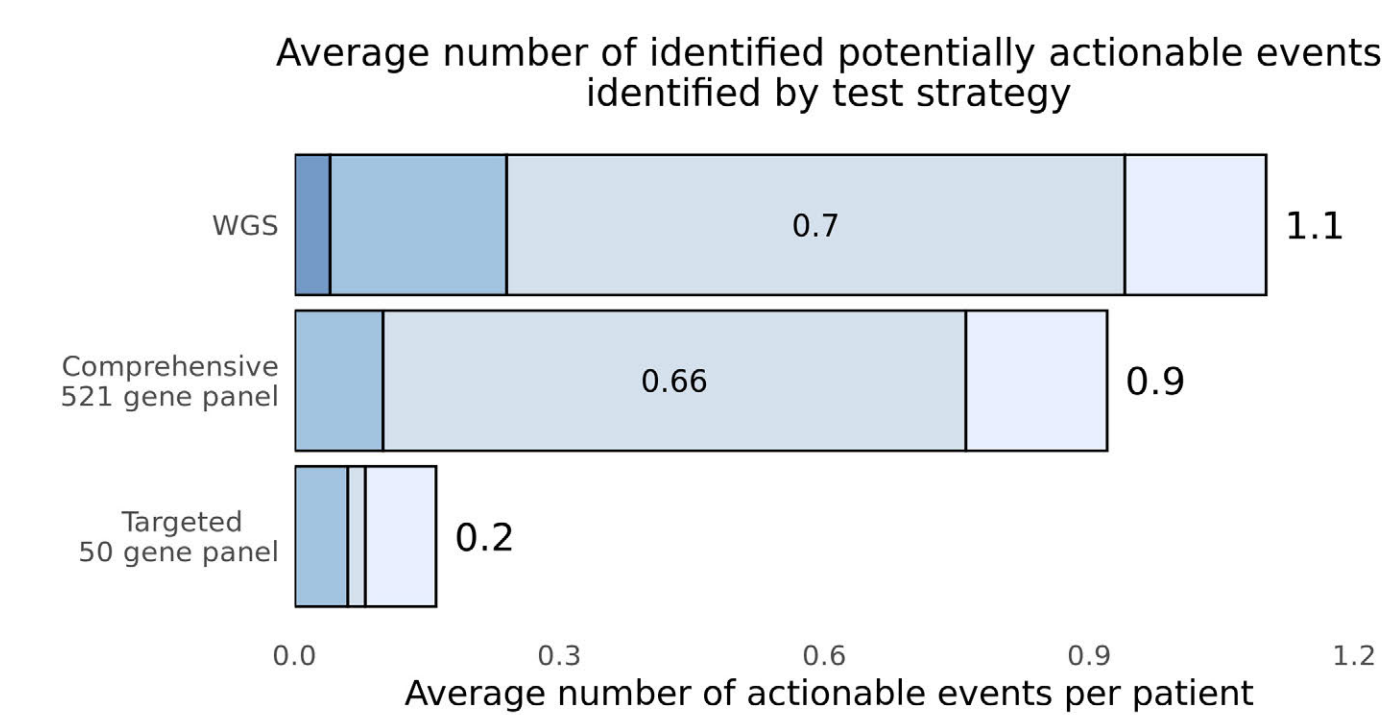| Gene | Type | Liposarcoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MDM2 | ONC | 64 | 3.3 | ▲ |
| CDK4 | ONC | 62 | 2 | ▲ |
| TERT | ONC | 22 | 13 | ▲ |
| FUS_DDIT3 | ONC | 20 | 0.1 | ▲ |
| ATRX | TSG | 16 | 2.4 | ▲ |
| TP53 | TSG | 16 | 55 | ▼ |
| RB1 | TSG | 12 | 11 | |
| PTEN | TSG | 10 | 14 | |
| MCL1 | ONC | 8 | 1.4 | ▲ |
| CDKN2A | TSG | 6 | 25 | ▼ |
| DDR2 | ONC | 6 | 0.6 | ▲ |
| LMBRD2 | ONC | 6 | 1 | ▲ |
| MYC | ONC | 6 | 5.7 | |
| NF1 | TSG | 6 | 7 | |
| PLCG1 | ONC | 6 | 0.6 | ▲ |
| PREX2 | ONC | 6 | 1.6 | ▲ |
| TOP1 | ONC | 6 | 0.6 | ▲ |
| ZNF217 | ONC | 6 | 2 | |
| CCND3 | ONC | 4 | 0.8 | ▲ |
| DOCK8 | TSG | 4 | 0.6 | ▲ |
| H3C13 | ONC | 4 | 0.9 | ▲ |
| IL7R | ONC | 4 | 0.9 | ▲ |
| PIK3CA | ONC | 4 | 13 | ▼ |
| PIM1 | ONC | 4 | 0.3 | ▲ |
| PTPRD | TSG | 4 | 3 | |
| ROS1 | ONC | 4 | 0.3 | ▲ |
| SMARCA4 | TSG | 4 | 2.5 | |
| TG | ONC | 4 | 2.3 | ▲ |
| AGBL1_NTRK3 | ONC | 2 | 0 | ▲ |

**Top cancer drivers** — 50 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events

**Actionable**: 18% None / 18% None ; 4% 3+ / 26% 3+ ; 78% 1-2 / 56% 1-2
**Best treatment option**: 18% None / 18% None ; 10% Oth / 14% Oth ; 54% Exp / 28% Exp ; 14% Off / 36% Off ; 4% FDA

### Summary

| Event | Liposarcoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDK4 | 60 | 1.9 | |
| PTEN | 10 | 13 | |
| CDKN2A | 6 | 24 | ▼ |
| PIK3CA | 4 | 13 | ▼ |
| AGBL1 - NTRK3 fusion | 2 | 0 | ▲ |
| ATM | 2 | 3.5 | |
| BRCA2 | 2 | 2.4 | |
| CCND1 | 2 | 5.3 | |
| CD274 | 2 | 0.5 | ▲ |
| FGFR1 | 2 | 3.8 | |
| HR deficiency | 2 | 5.8 | |
| KMT2D | 2 | 2.9 | |
| MAP3K5 - NTRK2 fusion | 2 | 0 | ▲ |
| NF2 | 2 | 1.6 | |
| NUDCD1 - NRG1 fusion | 2 | 0 | ▲ |
| PAWR - ROS1 fusion | 2 | 0 | ▲ |
| SUB1 - FGFR1 fusion | 2 | 0 | ▲ |
| VEGFA | 2 | 0.7 | ▲ |

**Top potential actionable events** — 41 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

**Germline drivers**: 98% None / 84% None ; 2% 1+ / 16% 1+

### Summary

| Gene | Type | Liposarcoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 2 | 0.5 | ▲ |

**Top potential germline drivers** — 1 Patients

Legend: SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

- WGS: 2, 8, 28, 5, 7
- Comprehensive 521 gene panel: 4, 33, 5, 8
- Targeted 50 gene panel: 2, 4, 43

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

- WGS: 0.7 / 1.1
- Comprehensive 521 gene panel: 0.66 / 0.9
- Targeted 50 gene panel: 0.2

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Fusion: 2

**Drug Repurposing**
- Fusion: 2
- Partial CN Loss: 2
- HRD: 1

**Experimental/Other Guidelines**
- Fusion: 1
- Partial CN Loss: 1

**Other**

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- Fusion: 2

**Drug Repurposing**
- Fusion: 2
- Partial CN Loss: 2
- Small Variant: 1
- HRD: 1
- Splice Site: 1

**Experimental/Other Guidelines**
- Full CN Gain: 32
- Fusion: 1
- Partial CN Loss: 1

**Other**
- Small Variant: 4

Number of Missed Events

# The Genomic And Actionability Landscape Of Bone And Soft Tissue Sarcoma

## Cohort Metadata

### Data availability
Number of patients with data

WGS 381
RNASeq 106
Age, Sex 136
Biopsy site 132
Pretreatment 127
Treatment 104 →
Response 87 →

### Patients with treatment and response data

Post-biopsy treatment | Responders
Chemo 37 | 13 (35%)
Multiple 22 | 5 (23%)
Targeted 30 | 0
Hormonal 2 | 0
Immuno 1 | 0
Radio 14 | 3 (21%)
Other 1 | 0
None or NA 1 | 0

## Tumor Characteristics

■ Sarcoma ■ Pan-Cancer

TMB High 4% 21%
MSI High 0% 2%
WGD 41% 56%
Diploid Proportion 46% 34%
GIE HLA LOH 18% 19%
GIE Overall 22% 26%
Viral Insertions 0% 3%
HRD 3% 6%

## Mutational Landscape

### Tumor purity
73% / 55%

### Clonal mutation fraction
89% / 95%

### Tumor mutational burden
1.9 / 4.2
High 4% / 21%
TMB per Megabase

### Variant types

SNV 10,846 / 5,043
INDEL 983 / 401
Structural 183 / 169
MNV 92 / 38

Number of variants | Quantile

### Telomere Length
1.4 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
4 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.057 / 0.15
0% / 2% Instable
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
8 / 16

### % Copy number alteration
36% / 54%

### % Genome LOH
20% / 24%

## Processes Underlying Mutations

UV light: 48%
Chemical exposure: 9%
DNA damage repair: 7%
Ageing: 5%
APOBEC: 3%
Tobacco: 1%
Unknown: 26%

Sarcoma
381 Patients

Pan-Cancer
6790 Patients

Bone | Soft tissue

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## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers

Somatic drivers: 6+ 19%, 1-5 79%
Oncogenes: None 18% 36%, 3+ 32% 20%, 1-2 50% 44%
TSGs: None 22%, 3+ 61% 38%, 1-2 33% 39%

| Gene | Type | Sarcoma (%) | Pan-Cancer (%) | Direction |
|------|------|------|------|------|
| TP53 | TSG | 42 | 55 | ▼ |
| RB1 | TSG | 28 | 11 | ▲ |
| CDKN2A | TSG | 21 | 25 | |
| ATRX | TSG | 14 | 2.4 | ▲ |
| MDM2 | ONC | 12 | 3.3 | ▲ |
| CDK4 | ONC | 11 | 2 | ▲ |
| PTEN | TSG | 7.3 | 14 | ▼ |
| TERT | ONC | 7.3 | 13 | ▼ |
| DMD | TSG | 5.2 | 3.5 | |
| NF1 | TSG | 5 | 5 | |
| KIT | ONC | 4.2 | 1.8 | ▲ |
| KDR | ONC | 3.9 | 0.8 | ▲ |
| PDGFRA | ONC | 3.7 | 0.8 | ▲ |
| NAB2_STAT6 | ONC | 3.1 | 0.2 | ▲ |
| MYC | ONC | 2.9 | 5.7 | |
| FUS_DDIT3 | ONC | 2.6 | 0.1 | ▲ |
| OR4F21 | TSG | 2.6 | 1.4 | |
| SS18_SSX1 | ONC | 2.6 | 0.1 | ▲ |
| PIK3CA | ONC | 2.4 | 13 | ▼ |
| SMARCB1 | TSG | 2.4 | 0.6 | ▲ |
| AR | ONC | 2.1 | 5.6 | |
| CSMD1 | TSG | 1.8 | 1.6 | |
| PREX2 | TSG | 1.8 | 1.6 | |
| CREBBP | TSG | 1.6 | 1.9 | |
| CYLD | TSG | 1.6 | 1.9 | |
| FGFR1 | TSG | 1.6 | 3.9 | |
| MCL1 | ONC | 1.6 | 1.4 | |
| MED12 | TSG | 1.6 | 1 | |
| PAX3_FOXO1 | ONC | 1.6 | 0.1 | ▲ |

321 Patients

■ AMPLIFICATION ■ DELETION ■ MUTATION ■ FUSION

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events

Actionable: None 18% 46%, 3+ 26% 6%, 1-2 56% 48%
Best treatment option: None 18% 46%, Oth 5% 20%, Off 28% 11%, Exp 17% 6%, FDA 36%

| Event | Sarcoma (%) | Pan-Cancer (%) | Direction |
|------|------|------|------|
| CDKN2A | 21 | 24 | |
| CDK4 | 10 | 1.9 | ▲ |
| PTEN | 7.3 | 13 | ▼ |
| TMB High | 3.9 | 21 | ▼ |
| CHEK2 | 3.4 | 3 | |
| HR deficiency | 3.1 | 5.8 | |
| PIK3CA | 2.1 | 13 | ▼ |
| FGFR1 | 1.6 | 3.8 | |
| TSC2 | 1.6 | 0.8 | |
| ATM | 1.3 | 3.5 | |
| CTNNB1 | 1.3 | 2.7 | |
| KMT2D | 1.3 | 2.9 | |
| CD274 | 1 | 0.5 | |
| NF2 | 1 | 1.6 | |
| AKT1 | 0.8 | 1.4 | |
| ASPSCR1 - TFE3 fusion | 0.8 | 0.1 | ▲ |
| BRAF | 0.8 | 5.9 | ▼ |
| BRCA1 | 0.8 | 1.3 | |
| BRCA2 | 0.8 | 2.4 | ▼ |
| BRIP1 | 0.8 | 0.4 | |
| EGFR | 0.8 | 5.1 | ▼ |
| ERBB4 | 0.8 | 0.5 | |
| KRAS | 0.8 | 14 | ▼ |
| Rest FDA | 1.8 | | |
| Rest Repurpose | 8.1 | | |
| Rest Experimental | 2.6 | | |
| Rest Other | 3.4 | | |

207 Patients

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events / Summary / Top potential germline drivers

Germline drivers: None 86% 84%, 1+ 14% 16%

| Gene | Type | Sarcoma (%) | Pan-Cancer (%) | Direction |
|------|------|------|------|------|
| CHEK2 | TSG | 3.1 | 3.2 | |
| BRCA1 | TSG | 1.6 | 1.1 | |
| MSH2 | TSG | 1.3 | 1 | |
| TP53 | TSG | 1.3 | 0.5 | |
| ATM | TSG | 1 | 1 | |
| MUTYH | TSG | 1 | 1.9 | |
| APC | TSG | 0.8 | 0.2 | ▲ |
| MSH6 | TSG | 0.8 | 0.4 | |
| NTHL1 | TSG | 0.8 | 0.4 | |

40 Patients

■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing
■ Other ■ None

### Highest evidence level treatment option identified by test strategy

WGS: 22 | 104 | 69 | 48 | 138
Comprehensive 521 gene panel: 16 | 63 | 70 | 49 | 183
Targeted 50 gene panel: 32 | 25 | 56 | 266

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

WGS: 0.36 | 0.28 | 0.35 | 1
Comprehensive 521 gene panel: 0.22 | 0.29 | 0.8
Targeted 50 gene panel: 0.22 | 0.4

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
Fusion 6

Drug Repurposing:
Partial CN Loss 37
HRD 12
Fusion 11
Full CN Gain 1

Experimental/Other Guidelines:
Partial CN Loss 15
Fusion 7
HMZ Disruption 1

Other:
Partial CN Loss 18
HMZ Disruption 3
Full CN Loss 2
Fusion 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved:
TMB High 15
Fusion 6

Drug Repurposing:
Small Variant 37
Partial CN Loss 37
HRD 12
Fusion 11
Splice Site 4

Experimental/Other Guidelines:
Full CN Gain 53
Partial CN Loss 15
Fusion 7
Full CN Loss 2
Small Variant 1

Other:
Small Variant 18
Partial CN Loss 18
Full CN Loss 5
Splice Site 4
HMZ Disruption 3

Number of Missed Events

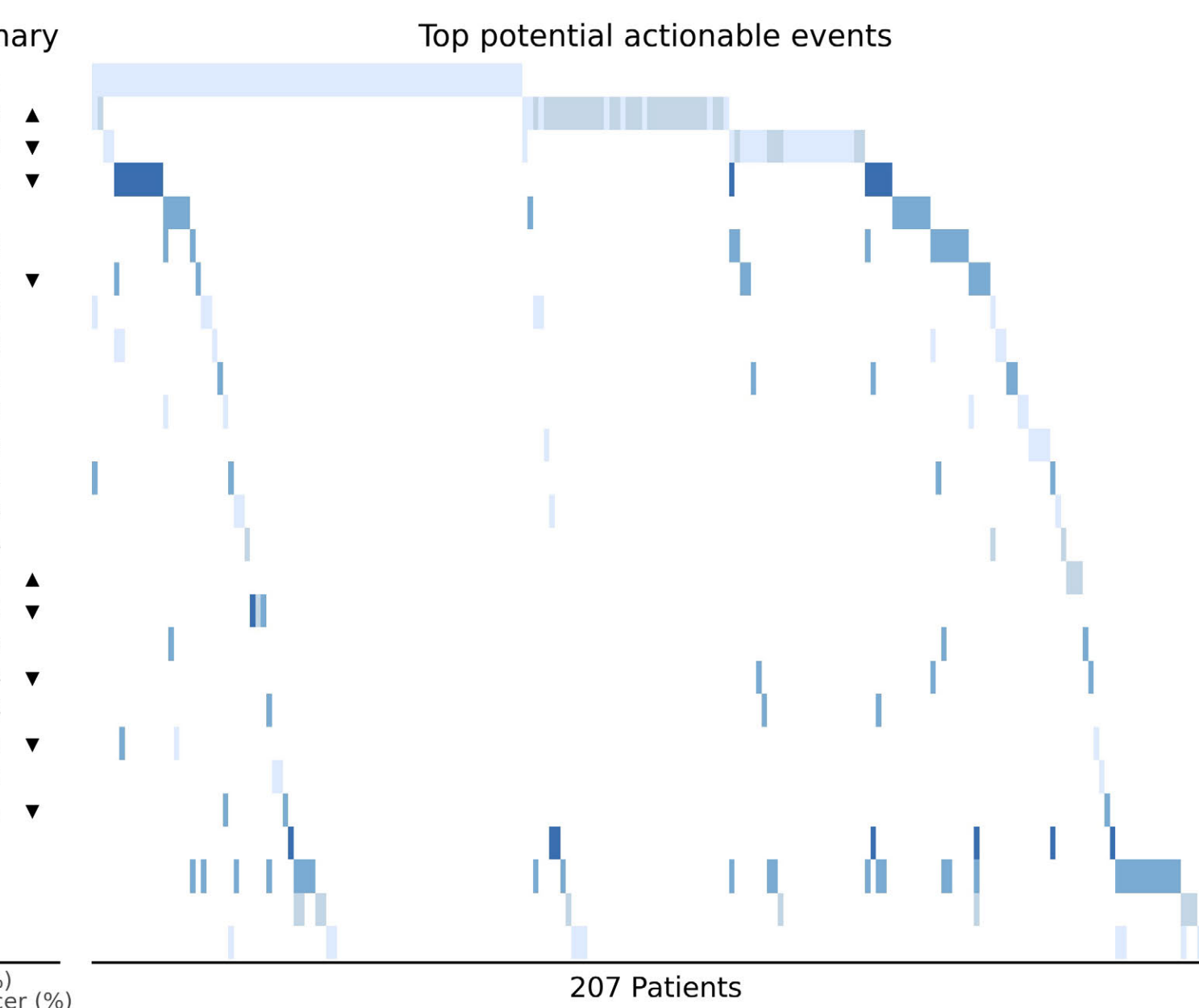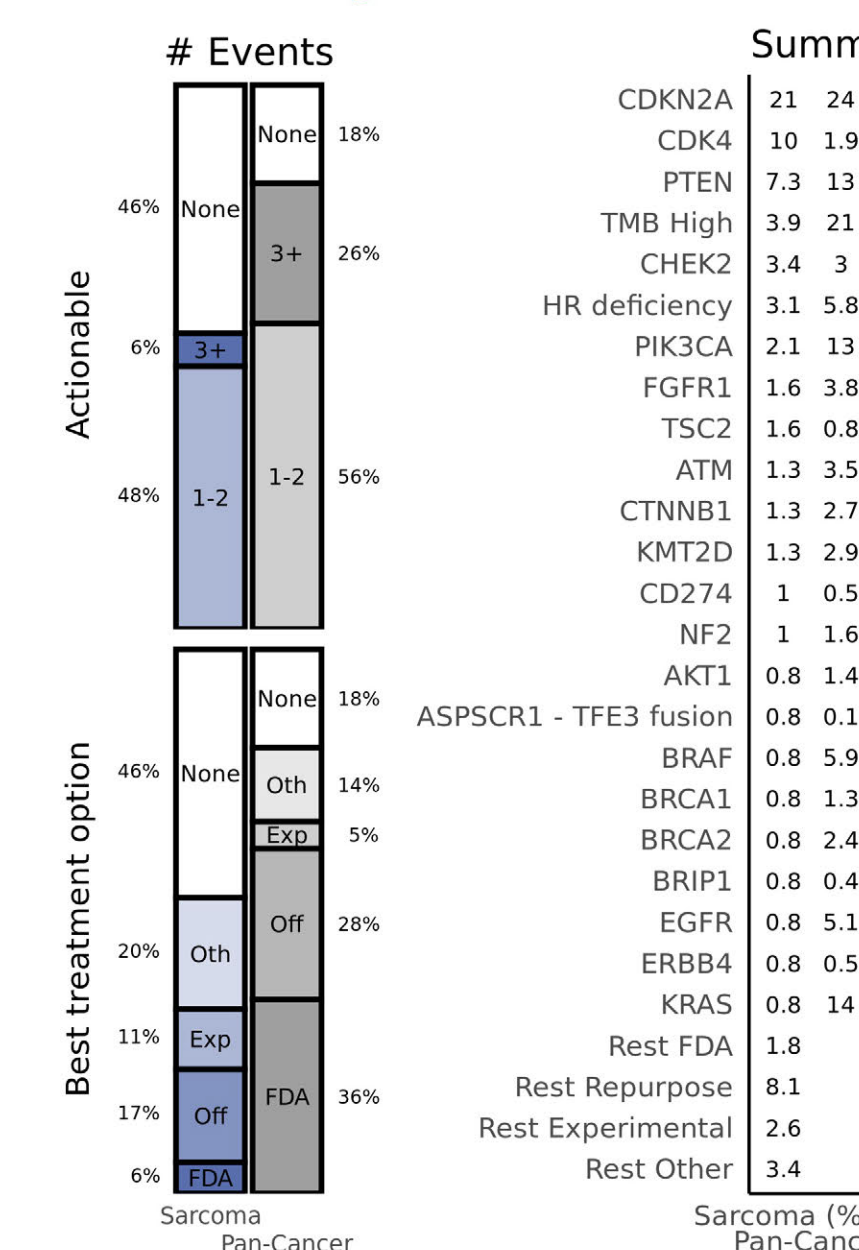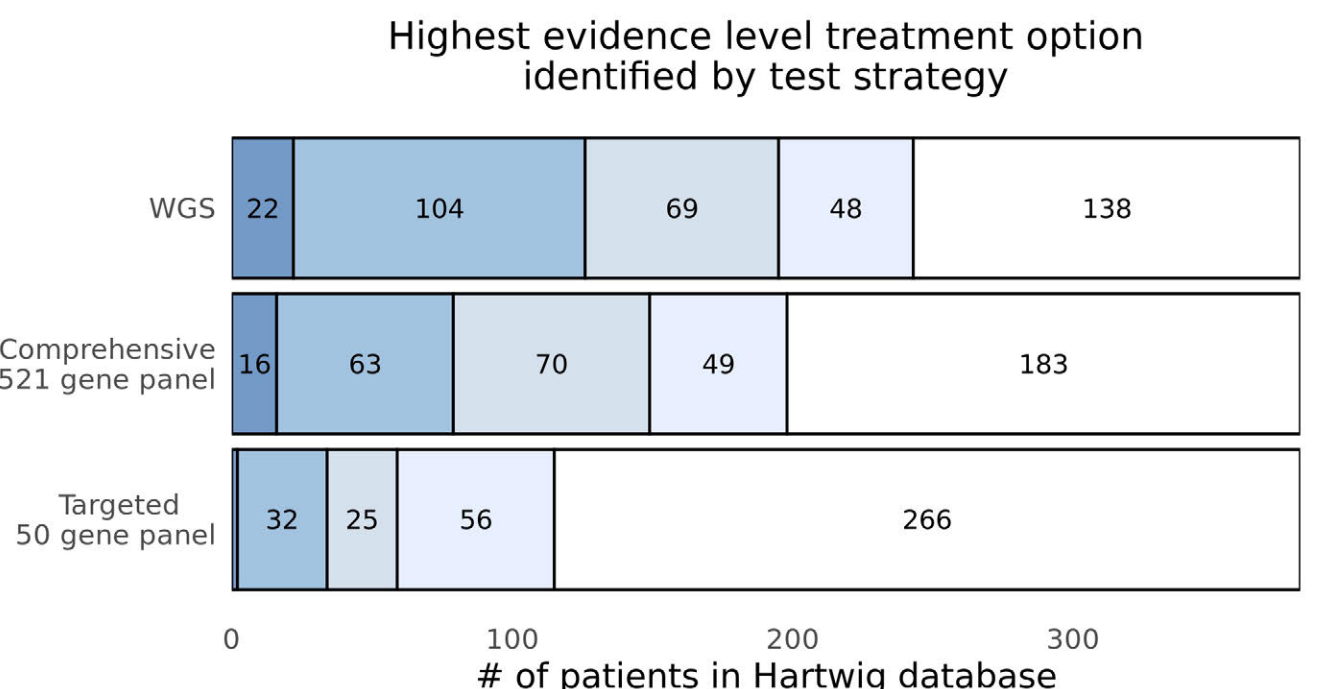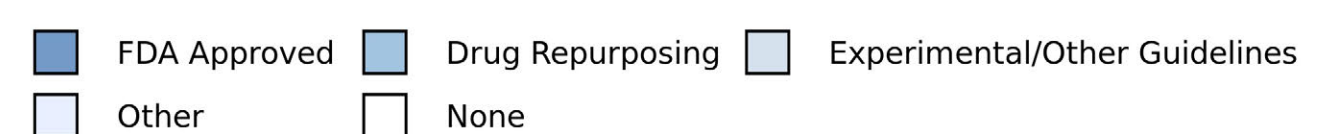## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Er+/Her2- Breast Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

- WGS — 612
- RNASeq — 416
- Age, Sex — 497
- Biopsy site — 486
- Pretreatment — 495
- Treatment — 470
- Response — 367 →

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

- Chemo — 141 / 47 (33%)
- Multiple — 166 / 55 (33%)
- Targeted — 12 / 3 (25%)
- Hormonal — 85 / 28 (33%)
- Immuno — 0 / 0
- Radio — 63 / 24 (38%)
- Other — 1 / 0
- None or NA — 0 / 0

## Processes Underlying Mutations

- APOBEC: 46%
- DNA damage repair: 14%
- Ageing: 7%
- Chemical exposure: 7%
- Tobacco: 1%
- UV light: 1%
- Unknown: 24%

## Cancer Driver Landscape

### # Events / Summary

Somatic drivers — 54% 6+ / 44% 6+ ; 45% 1-5 / 54% 1-5
Oncogenes — 7% None / 18% None ; 56% 3+ / 32% 3+ ; 37% 1-2 / 50% 1-2
TSGs — 9% None / 9% None ; 50% 3+ / 61% 3+ ; 41% 1-2 / 33% 1-2

| Gene | Type | Breast ER+/HER2- (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| PIK3CA | ONC | 45 | 13 | ▲ |
| TP53 | TSG | 33 | 55 | ▼ |
| ESR1 | ONC | 24 | 2.7 | ▲ |
| CCND1 | ONC | 23 | 5.6 | ▲ |
| FGF3 | ONC | 23 | 5.2 | ▲ |
| ZNF703 | ONC | 19 | 3.4 | ▲ |
| FGFR1 | ONC | 17 | 3.9 | ▲ |
| CDH1 | TSG | 15 | 2.8 | ▲ |
| GATA3 | TSG | 15 | 2.4 | ▲ |
| MAP2K4 | TSG | 15 | 3.9 | ▲ |
| RSF1 | TSG | 15 | 1.4 | |
| PTEN | TSG | 15 | 14 | |
| MYC | ONC | 11 | 5.7 | |
| NF1 | TSG | 9.8 | 7 | |
| KMT2C | TSG | 9 | 3.7 | ▲ |
| MAP3K1 | TSG | 8.5 | 1.1 | ▲ |
| ZNF217 | ONC | 8.3 | 2 | ▲ |
| RAD21 | ONC | 8.2 | 2.6 | |
| CDKN2A | TSG | 7.4 | 25 | ▼ |
| PPM1D | ONC | 6.9 | 1.7 | ▲ |
| AKT1 | ONC | 6.7 | 1.6 | ▲ |
| ANK1 | ONC | 6.5 | 2.4 | |
| USP32 | ONC | 6.5 | 1.5 | |
| PABPC1 | ONC | 6.4 | 2.3 | |
| MDM2 | ONC | 5.7 | 3.3 | |
| TG | ONC | 5.7 | 2.3 | |
| ZBTB10 | ONC | 5.6 | 2.1 | |
| ARID1A | TSG | 5.4 | 4.5 | |
| RB1 | TSG | 5.4 | 11 | ▼ |

**Top cancer drivers** — 599 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange)

## Tumor Characteristics

Legend: Breast ER+/HER2- (dark blue), Pan-Cancer (grey)

| Metric | Breast ER+/HER2- | Pan-Cancer |
|---|---|---|
| TMB High | 10% | 21% |
| MSI High | 1% | 2% |
| WGD | 49% | 56% |
| Diploid Proportion | 37% | 34% |
| GIE HLA LOH | 13% | 19% |
| GIE Overall | 19% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 9% | 6% |

## Mutational Landscape

**Tumor purity** — 59% / 55%
**Clonal mutation fraction** — 94% / 95%
**Tumor mutational burden** — 2.8 / 4.2 ; High 10% / 21% ; TMB per Megabase

### Variant types (Number of variants by Quantile)

- SNV — 10,846 / 7,153
- INDEL — 983 / 626 ; 183
- Structural — 208 / 183
- MNV — 92 / 45

- Telomere Length — 0.7 / 0.82 — Log2 (Tumor/Germline length)
- VDJ CDR3 Sequences — 5 / 6 — Log2 (CDR3 + 1)
- Microsatellite instability — 0.1 / 0.15 ; Instable 1% / 2% — MS indels per megabase

- Mean genome ploidy — 2.3 / 2.6
- Aneuploidy Score — 13 / 16
- % Copy number alteration — 46% / 54%
- % Genome LOH — 20% / 24%

## Copy Number Alteration Profile

Genes labelled: TP53, SMAD4, PPM1D, PRDM1, USP9, NF1, MAP2K4, TP53, CDH1, CBFB, FOXP1, RB1, MDM2, RSF1, FGF3, CCND1, LINC00881, PTEN, CDKN2A, PTPN12, JAK2, FGFR1, ORMDL1, CSMD3, FOXO3, AFDN

## Potentially Actionable Events

### # Events / Summary

Actionable — 8% None / 18% None ; 33% 3+ / 26% 3+ ; 58% 1-2 / 56% 1-2
Best treatment option — 8% None / 18% None ; 10% Oth / 14% Oth ; 17% Exp / 5% Exp ; 48% Off / 28% Off ; 17% FDA / 36% FDA

| Gene | Breast ER+/HER2- (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PIK3CA | 44 | 13 | ▲ |
| ESR1 | 22 | 2.3 | ▲ |
| CCND1 | 22 | 5.3 | ▲ |
| FGFR1 | 16 | 3.8 | ▲ |
| PTEN | 15 | 13 | |
| TMB High | 9.5 | 21 | ▼ |
| HR deficiency | 9 | 5.8 | |
| CHEK2 | 7.5 | 3 | |
| CDKN2A | 7.4 | 24 | ▼ |
| AKT1 | 6.4 | 1.4 | ▲ |
| BRCA2 | 5.7 | 2.4 | |
| ATM | 4.2 | 3.5 | |
| ERBB2 | 3.8 | 5.6 | |
| FGFR2 | 2.9 | 1.1 | |
| KRAS | 2.3 | 14 | ▼ |
| IGF1R | 1.5 | 0.4 | ▲ |
| CDK4 | 1.3 | 1.9 | |
| FGFR3 | 1.3 | 1.2 | |
| TSC1 | 1.1 | 1.1 | |
| BRAF | 1.1 | 5.9 | ▼ |
| KMT2D | 1.1 | 2.9 | |
| MSI High | 1 | 3.1 | ▼ |
| BRCA1 | 0.7 | 1.3 | |
| Rest FDA | 1.3 | | |
| Rest Repurpose | 7.7 | | |
| Rest Experimental | 2.8 | | |
| Rest Other | 4.1 | | |

**Top potential actionable events** — 560 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

Germline drivers — 79% None / 84% None ; 21% 1+ / 16% 1+

| Gene | Type | Breast ER+/HER2- (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 7.2 | 3.2 | |
| BRCA2 | TSG | 5.1 | 1.5 | ▲ |
| MUTYH | TSG | 2.1 | 1.9 | |
| ATM | TSG | 1.5 | 1 | |
| MSH2 | TSG | 1 | 1 | |
| BRCA1 | TSG | 0.7 | 1.1 | |
| RAD50 | TSG | 0.7 | 0.5 | |
| MITF | ONC | 0.5 | 0.7 | |
| NTHL1 | TSG | 0.5 | 0.4 | |

**Top potential germline drivers** — 113 Patients

Legend: STRUCTURAL_VARIANT (blue), SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

(# of patients in Hartwig database)

- WGS — 104 / 297 / 148 / 24 / 39
- Comprehensive 521 gene panel — 100 / 272 / 159 / 24 / 57
- Targeted 50 gene panel — 284 / 70 / 32 / 217

### Average number of identified potentially actionable events identified by test strategy

(Average number of actionable events per patient)

- WGS — 0.2 / 0.95 / 0.89 / 0.28 = 2.3
- Comprehensive 521 gene panel — 0.78 / 0.75 / 0.23 = 2
- Targeted 50 gene panel — 0.56 / 0.2 = 0.9

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Fusion — 4

**Drug Repurposing**
- HRD — 55
- Fusion — 23
- Partial CN Loss — 17
- HMZ Disruption — 7
- Partial CN Gain — 1

**Experimental/Other Guidelines**
- Partial CN Loss — 55
- Fusion — 15
- Partial CN Gain — 8
- Full CN Gain — 4
- HMZ Disruption — 1

**Other**
- Partial CN Loss — 14
- Full CN Loss — 7
- Small Variant — 4
- HMZ Disruption — 3

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- TMB High — 58
- Small Variant — 44
- Splice Site — 6
- Fusion — 4
- Full CN Loss — 2

**Drug Repurposing**
- Small Variant — 130
- HRD — 55
- Fusion — 23
- Partial CN Loss — 17
- HMZ Disruption — 7

**Experimental/Other Guidelines**
- Full CN Gain — 178
- Small Variant — 141
- Partial CN Loss — 55
- Full CN Loss — 21
- Fusion — 15

**Other**
- Small Variant — 57
- Partial CN Loss — 14
- Splice Site — 9
- Full CN Loss — 8
- HMZ Disruption — 4

(Number of Missed Events)

## Tumor figures

Breast ER+/HER2- 612 Patients — Pan-Cancer 6790 Patients — Breast

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# The Genomic And Actionability Landscape Of Her2-Positive Breast Cancer

A full-size scientific poster presenting genomic and actionability analysis of HER2-positive breast cancer, with the following panels:

## Cohort Metadata

**Data availability** — Number of patients with data: WGS 127, RNASeq 95, Age/Sex 109, Biopsy site 107, Pretreatment 108, Treatment 99, Response 86.

**Patients with treatment and response data** — Post-biopsy treatment: Chemo 13, Multiple 59, Targeted 12, Hormonal 4, Immuno 1, Radio 22, Other 0, None or NA 0. Responders: 3 (23%), 32 (54%), 5 (42%), 1 (100%), 13 (59%).

## Tumor Characteristics

Breast HER2+ vs Pan-Cancer: TMB High 10%/21%, MSI High 0%/2%, WGD 70%/56%, Diploid Proportion 24%/34%, GIE HLA LOH 12%/19%, GIE Overall 18%/26%, Viral Insertions 0%/3%, HRD 7%/6%.

## Mutational Landscape

Tumor purity 52%/55%; Clonal mutation fraction 97%/95%; Tumor mutational burden 4/4.2, 10%/21% High.

Variant types: SNV 10,846/10,309; INDEL 983/873; Structural 512/183; MNV 92/68.

Telomere Length 0.69/0.82; VDJ CDR3 Sequences 6/6; Microsatellite instability 0.14/0.15, 0%/2% Instable.

Mean genome ploidy 3/2.6; Aneuploidy Score 21/16; % Copy number alteration 68%/54%; % Genome LOH 22%/24%.

## Processes Underlying Mutations

APOBEC: 41%, Chemical exposure: 10%, DNA damage repair: 10%, Ageing: 5%, Tobacco: 4%, UV light: 2%, Unknown: 28%.

Breast HER2+ 127 Patients / Pan-Cancer 6790 Patients

## Cancer Driver Landscape

Top cancer drivers — 127 Patients. AMPLIFICATION / DELETION / MUTATION.

| Gene | Type | Breast HER2+ (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| ERBB2 | ONC | 72 | 5.7 | ▲ |
| TP53 | TSG | 61 | 55 | |
| PIK3CA | ONC | 40 | 13 | |
| MYC | ONC | 23 | 5.7 | ▲ |
| PPM1D | ONC | 19 | 1.7 | ▲ |
| SPOP | ONC | 19 | 1.3 | ▲ |
| ZNF703 | ONC | 19 | 3.4 | ▲ |
| USP32 | ONC | 18 | 1.5 | ▲ |
| RAD21 | ONC | 17 | 2.6 | ▲ |
| CCND1 | ONC | 16 | 5.6 | |
| FGF3 | ONC | 15 | 5.2 | ▲ |
| FGFR1 | ONC | 13 | 3.9 | ▲ |
| PABPC1 | ONC | 13 | 2.3 | ▲ |
| TOP2A | ONC | 13 | 1 | ▲ |
| MAP2K4 | TSG | 11 | 3.9 | ▲ |
| CD79B | ONC | 10 | 0.8 | ▲ |
| CDKN2A | TSG | 10 | 25 | ▼ |
| TG | ONC | 10 | 2.6 | ▲ |
| ZBTB10 | ONC | 9.4 | 2.1 | ▲ |
| ZNF217 | ONC | 9.4 | 2.2 | ▲ |
| CDH1 | TSG | 8.7 | 2.8 | ▲ |
| CRYBG1 | ONC | 8.7 | 1 | ▲ |
| RSF1 | ONC | 8.7 | 2.4 | ▲ |
| ANK1 | ONC | 7.9 | 2.4 | ▲ |
| PREX2 | ONC | 7.9 | 1.6 | ▲ |
| KMT2C | TSG | 7.1 | 3.7 | |
| NCOA2 | ONC | 7.1 | 1.6 | ▲ |
| GATA3 | TSG | 6.3 | 1.8 | ▲ |
| PTEN | TSG | 6.3 | 14 | ▼ |

# Events: Somatic drivers 74% 6+, 26% 1-5; Oncogenes 80% 3+, 19% 1-2; TSGs 39% 3+, 50% 1-2. Summary 44% 6+, 18% None; 32% 3+, 50% 1-2; 61% 3+, 33% 1-2.

## WGS vs Panel Coverage

FDA Approved / Drug Repurposing / Other / Experimental/Other Guidelines / None

**Highest evidence level treatment option identified by test strategy** — WGS: 96, 21, 8; Comprehensive 521 gene panel: 96, 19, 9; Targeted 50 gene panel: 85, 24, 4, 5, 9.

**Average number of identified potentially actionable events identified by test strategy** — WGS: 0.8, 0.9, 0.38, 0.21 = 2.3; Comprehensive 521 gene panel: 0.8, 0.72, 0.28 = 2; Targeted 50 gene panel: 0.67, 0.45 = 1.3.

**Top missed events by Comprehensive Panel vs WGS** — FDA Approved; Drug Repurposing: HRD 9, Fusion 8, Partial CN Loss 4, HMZ Disruption 2; Experimental/Other Guidelines: Partial CN Loss 9, Partial CN Gain 3; Other: HMZ Disruption 2, Partial CN Loss 1.

**Top missed events by Targeted Panel vs WGS** — FDA Approved: TMB High 13, Small Variant 2, Full CN Loss 1, Splice Site 1; Drug Repurposing: Small Variant 31, HRD 9, Fusion 8, Partial CN Loss 4, Splice Site 3; Experimental/Other Guidelines: Full CN Gain 17, Partial CN Loss 9, Full CN Loss 4, Partial CN Gain 4, Small Variant 2; Other: Small Variant 8, HMZ Disruption 2, Partial CN Loss 1.

## Potentially Actionable Events

Top potential actionable events — 124 Patients. FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other.

| Event | Breast HER2+ (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| ERBB2 | 71 | 5.6 | ▲ |
| PIK3CA | 40 | 13 | ▲ |
| CCND1 | 16 | 5.3 | ▲ |
| FGFR1 | 13 | 3.8 | ▲ |
| CDKN2A | 10 | 24 | ▼ |
| TMB High | 10 | 21 | ▼ |
| CHEK2 | 7.1 | 3 | |
| HR deficiency | 7.1 | 5.8 | |
| PTEN | 5.5 | 13 | ▼ |
| CDK12 | 3.9 | 0.9 | ▲ |
| ESR1 | 3.9 | 2.3 | |
| KRAS | 3.9 | 14 | ▼ |
| ATM | 3.1 | 3.5 | |
| AKT1 | 2.4 | 1.4 | |
| BRCA2 | 2.4 | 2.4 | |
| FLT4 | 2.4 | 0.1 | ▲ |
| EGFR | 1.6 | 5.1 | ▼ |
| ERBB3 | 1.6 | 0.5 | ▲ |
| IGF1R | 1.6 | 0.4 | ▲ |
| ADAM32 - FGFR1 fusion | 0.8 | 0 | ▲ |
| AR | 0.8 | 2.8 | ▼ |
| BAG4 - FGFR1 fusion | 0.8 | 0 | ▲ |
| BCAS3 - FGFR1 fusion | 0.8 | 0 | ▲ |
| Rest FDA | | | |
| Rest Repurpose | 7.9 | | |
| Rest Experimental | 0.8 | | |
| Rest Other | 3.1 | | |

# Events — Actionable: 37% 3+, 61% 1-2; Best treatment option: 4% None, 17% Off, 76% FDA. Summary: 18% None, 26% 3+, 56% 1-2; 18% None, 14% Oth, 28% Off, 36% FDA.

## Copy Number Alteration Profile

(circular CNA genome plot with gene labels)

## Germline Predisposition

Top potential germline drivers — 19 Patients. SMALL_VARIANT.

| Gene | Type | Breast HER2+ (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 7.1 | 3.2 | |
| ATM | TSG | 1.6 | 1 | |
| MITF | ONC | 1.6 | 0.7 | |
| MUTYH | TSG | 1.6 | 1.9 | |
| BRCA2 | TSG | 0.8 | 1.5 | |
| CDK12 | TSG | 0.8 | 0.1 | ▲ |
| EPCAM | TSG | 0.8 | 0.1 | ▲ |
| MSH6 | TSG | 0.8 | 0.4 | |
| RAD50 | TSG | 0.8 | 0.5 | |

# Events — Germline drivers: 82% None, 18% 1+. Summary: 84% None, 16% 1+.

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the % percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3x sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).
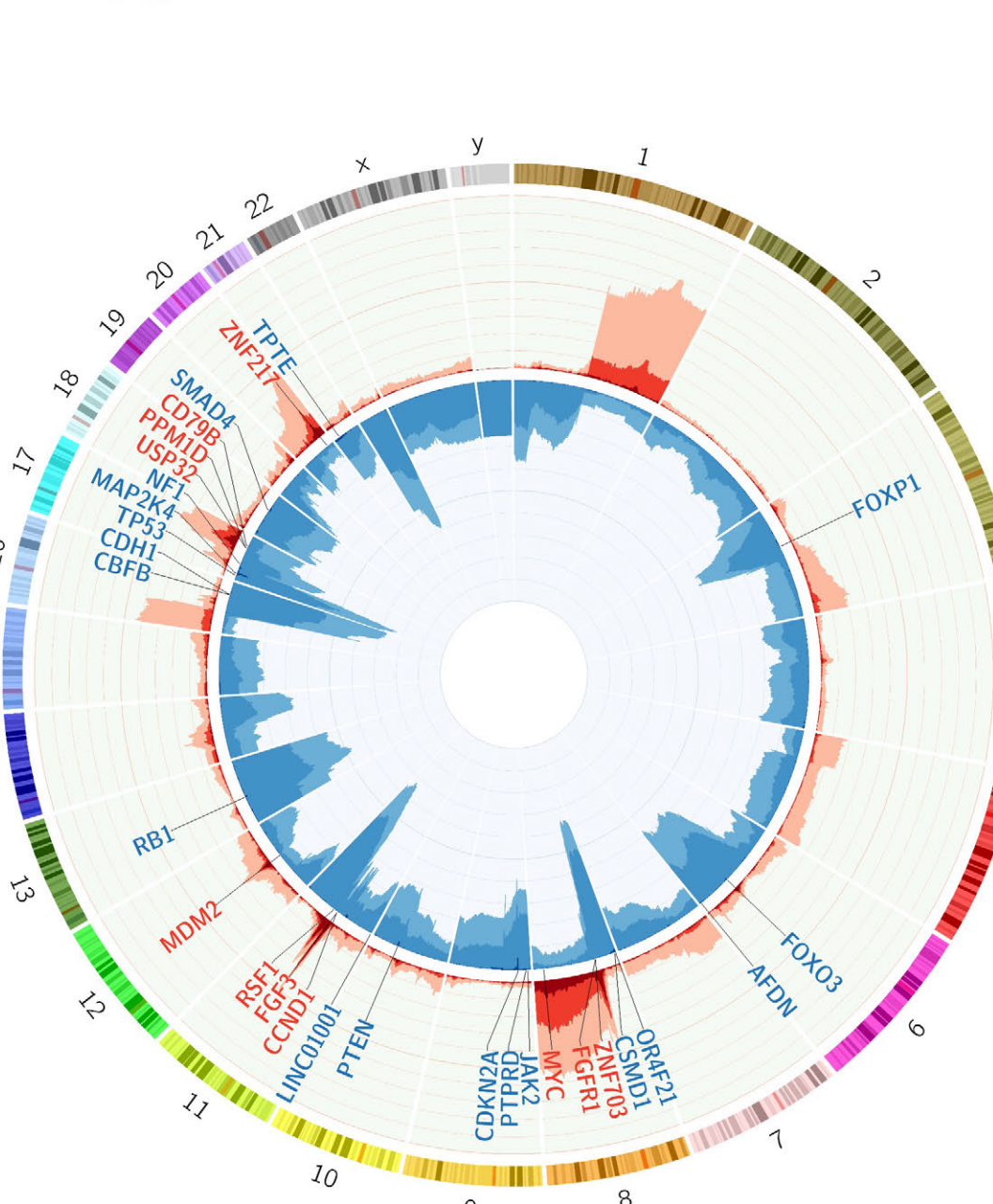
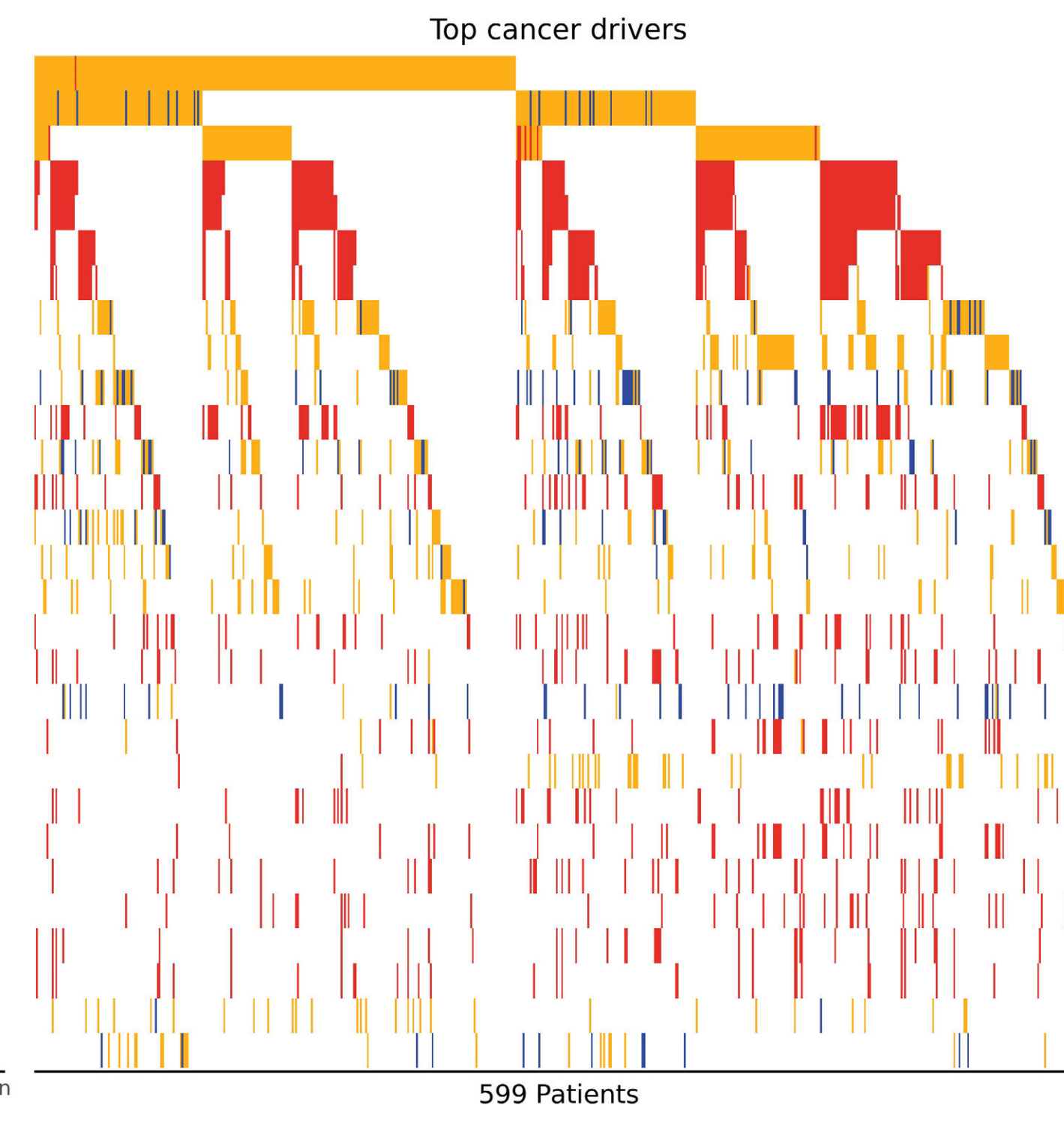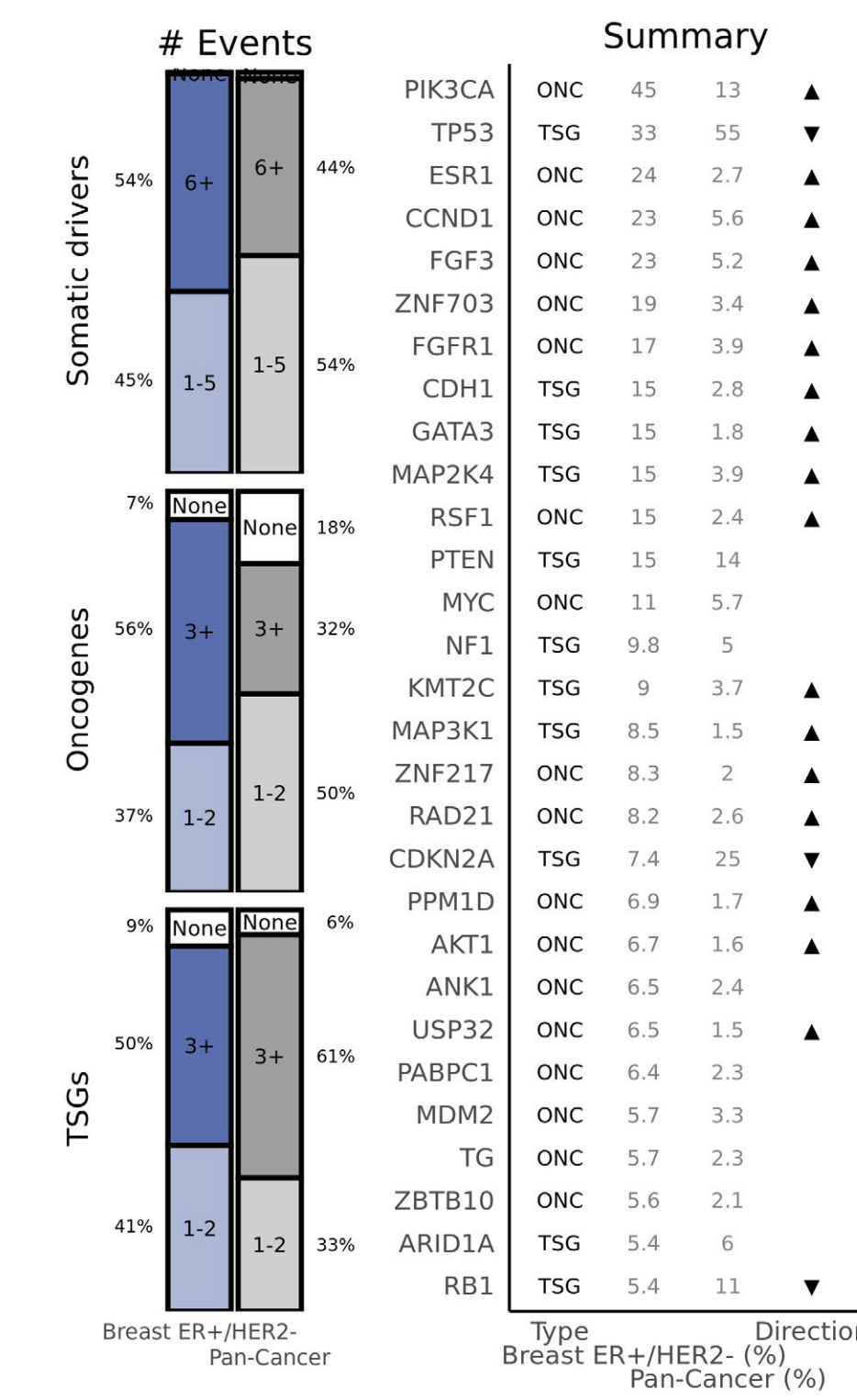Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.
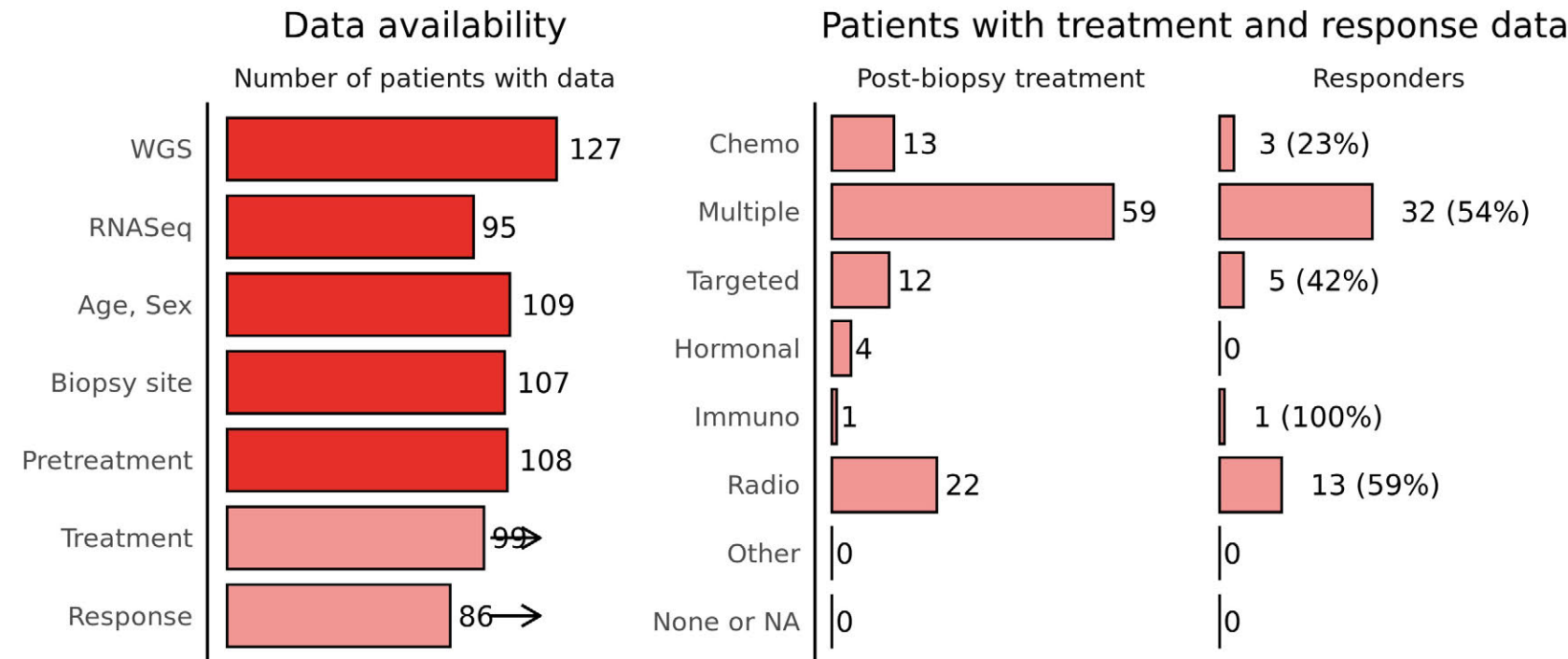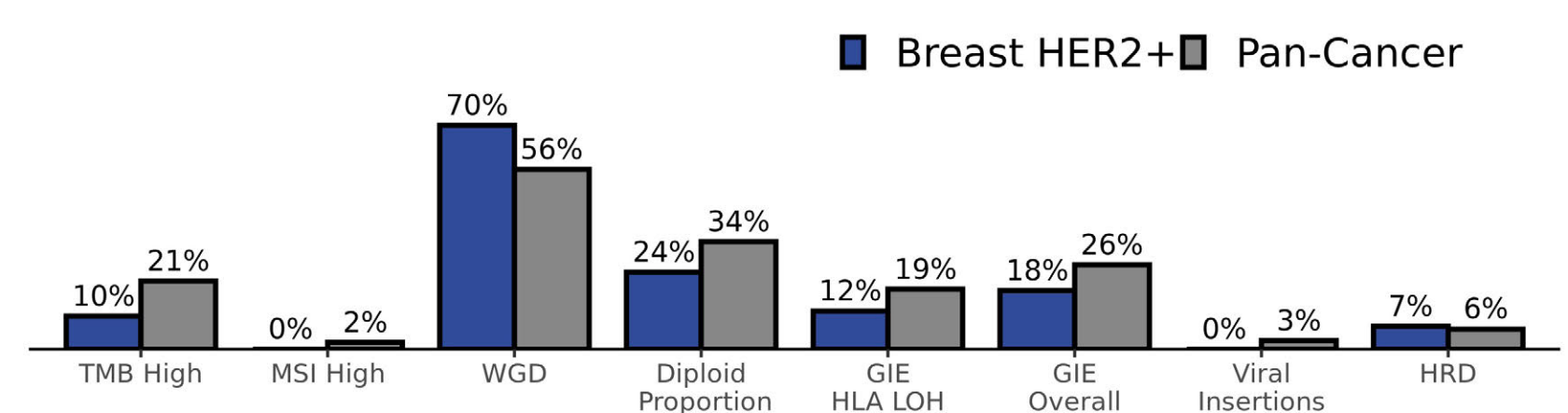
WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with: Full CN Loss < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Distruptions, Viral Inserts, HLA copy number. HLA assumed not captured by panels.
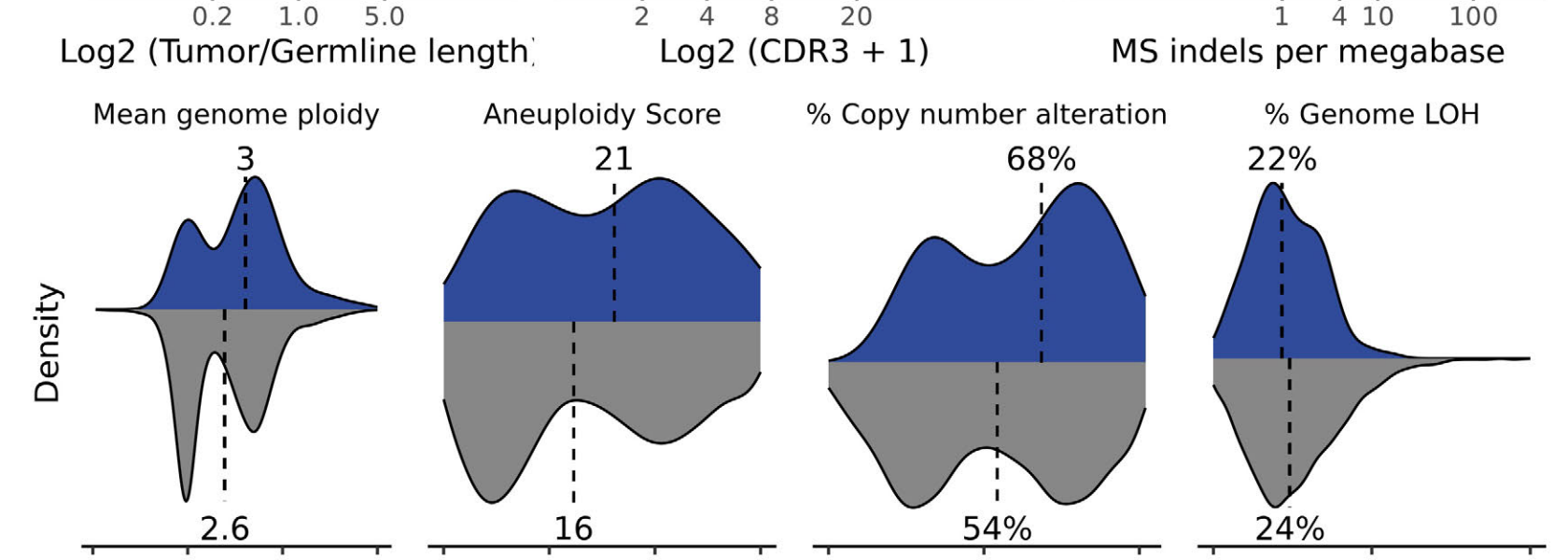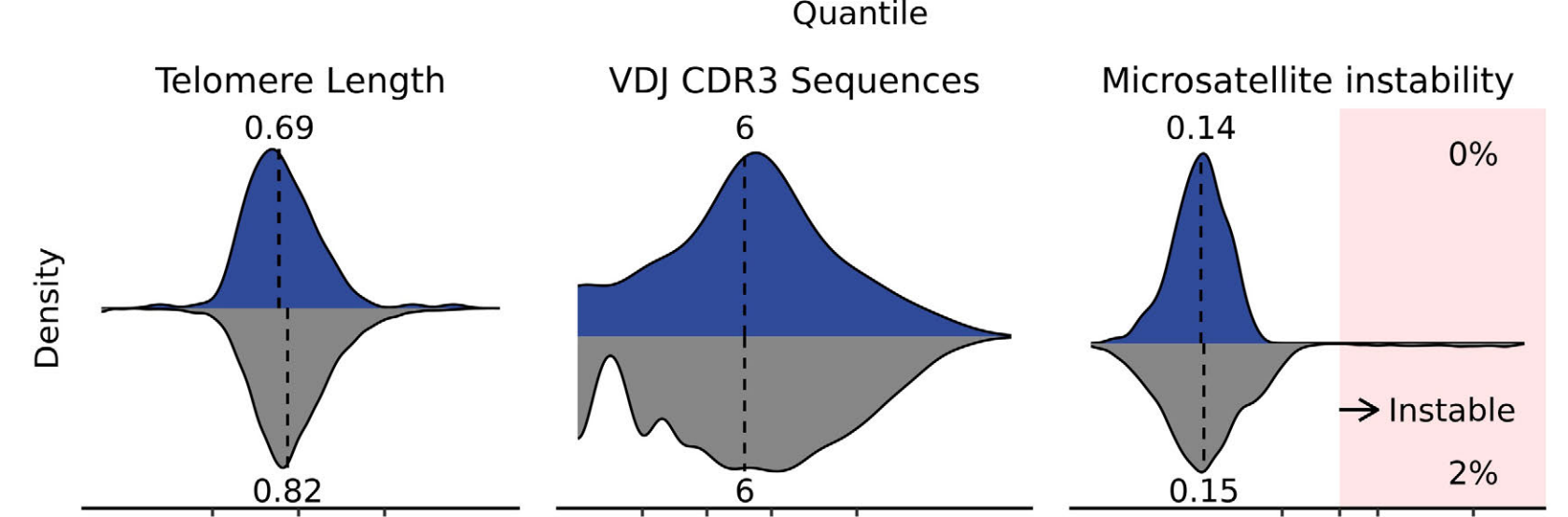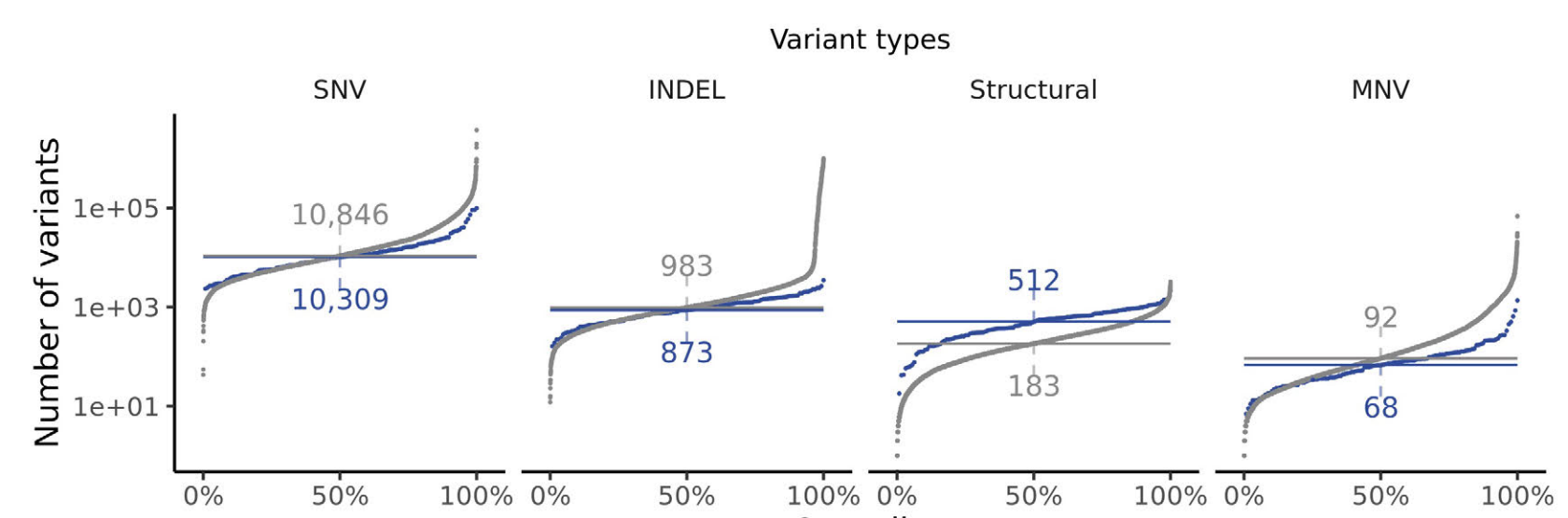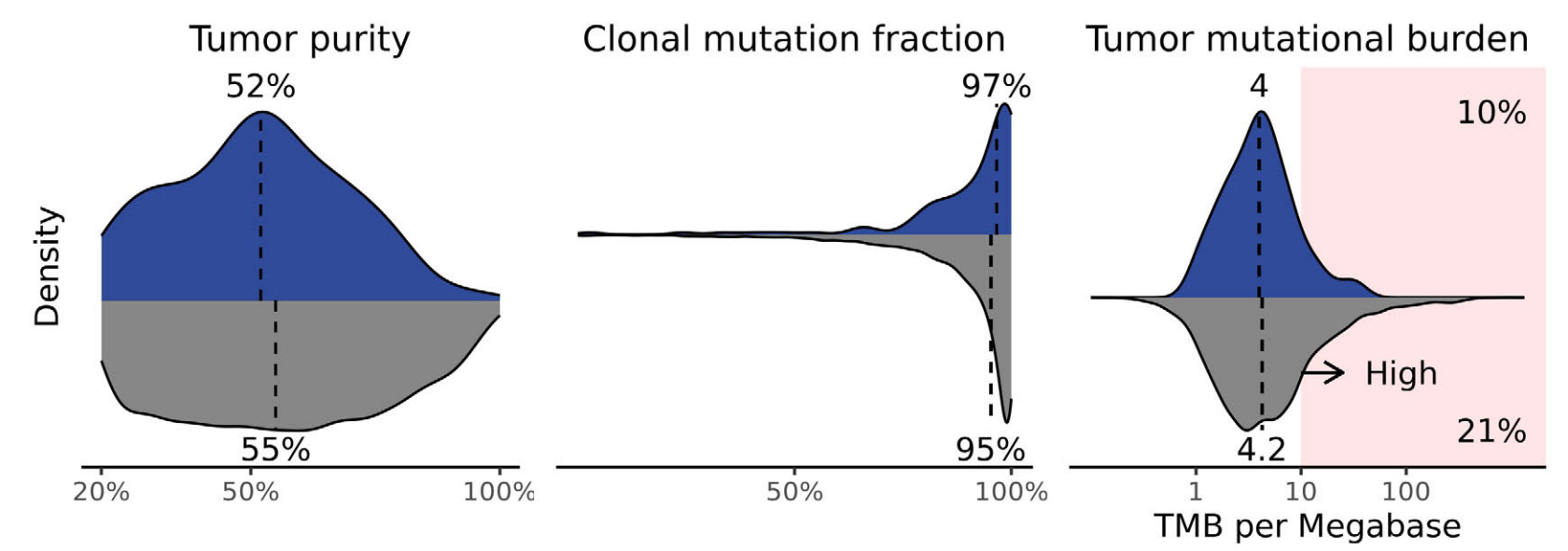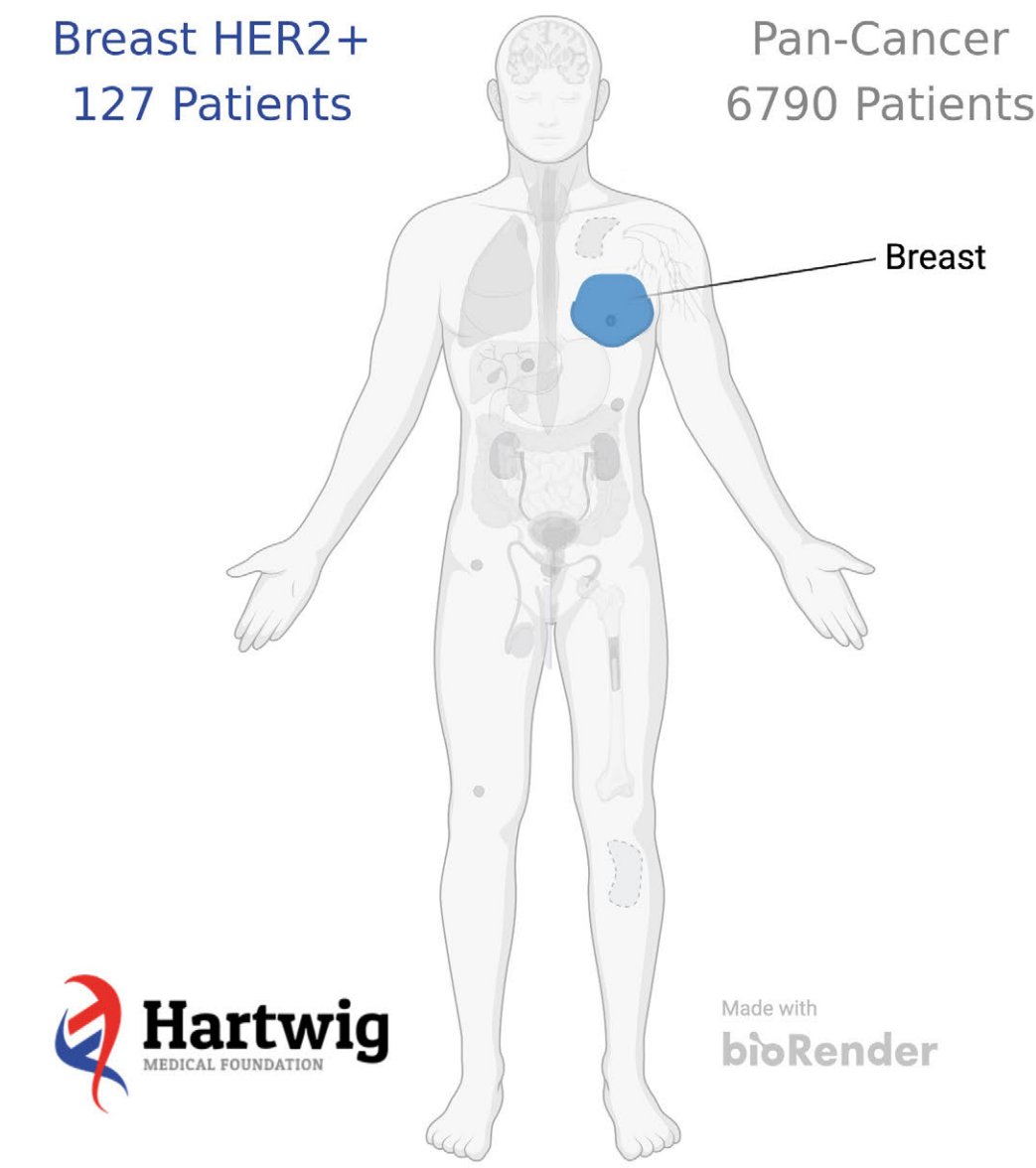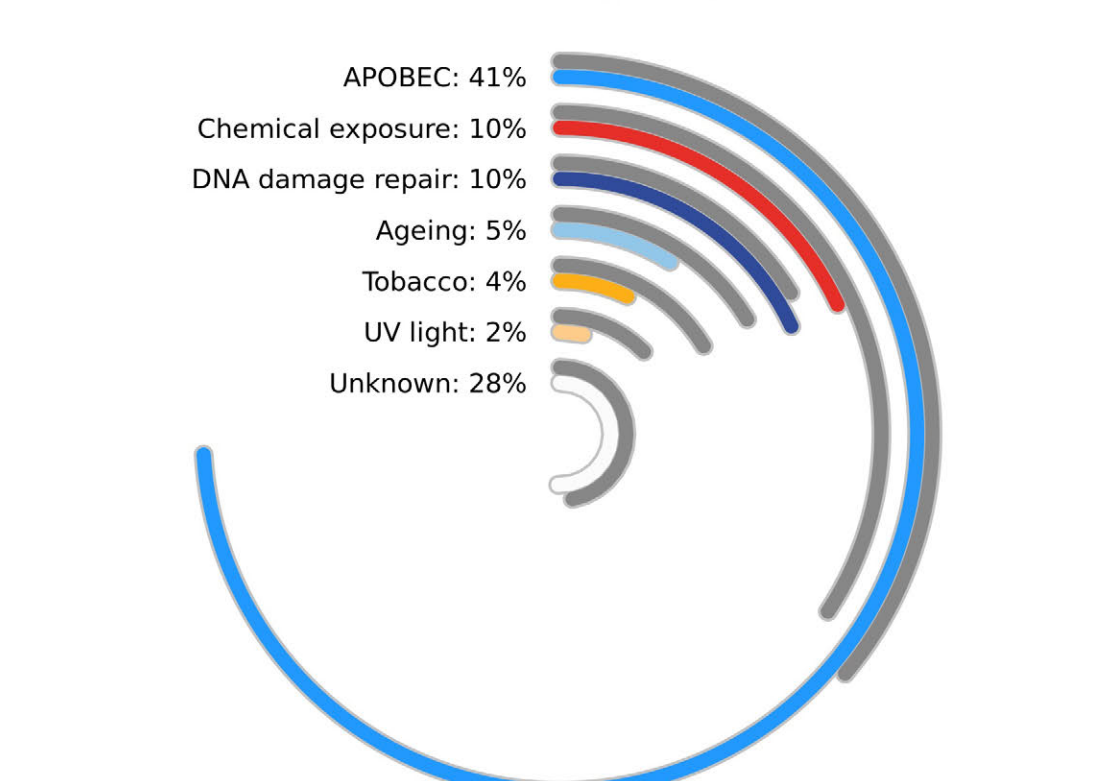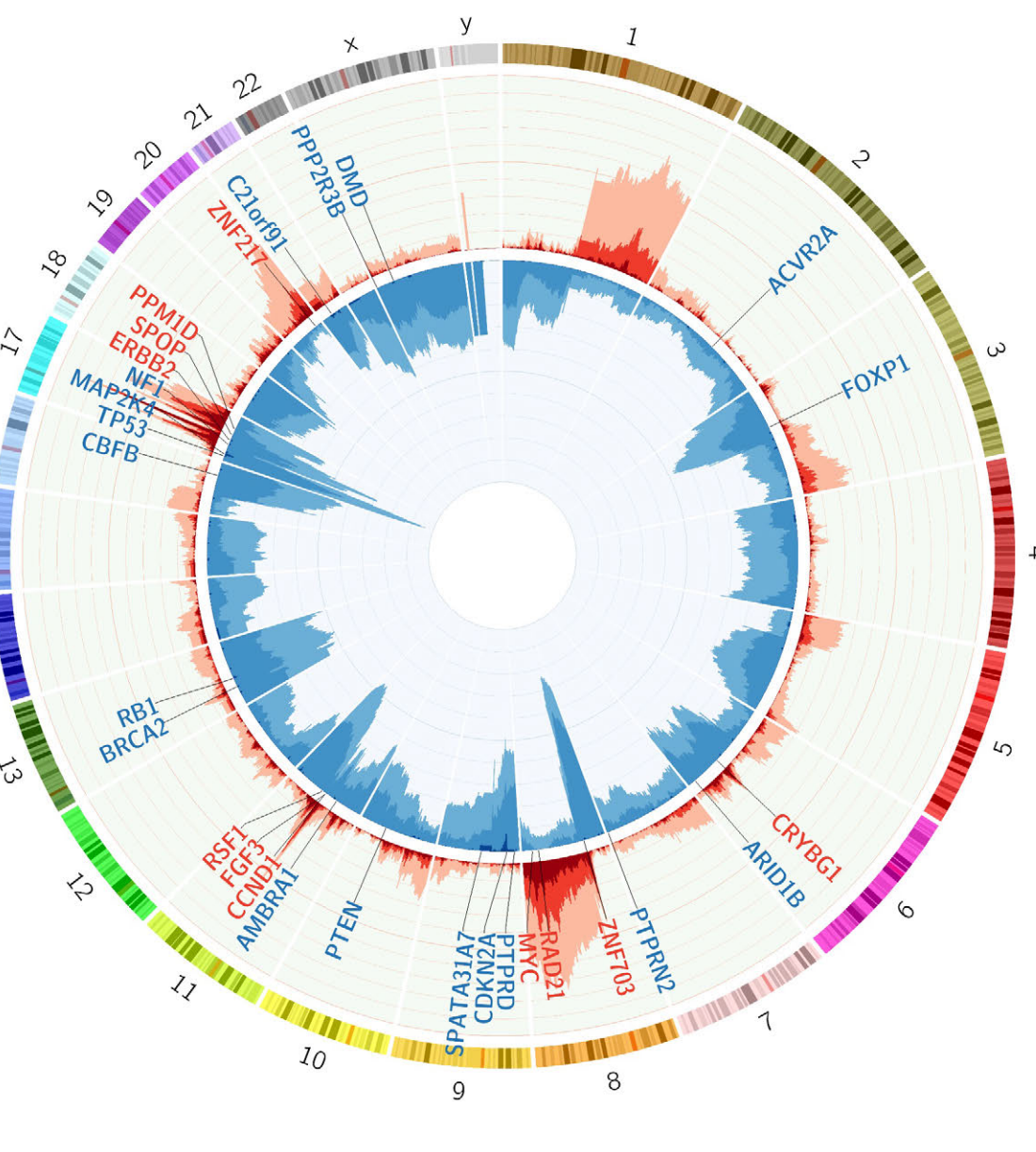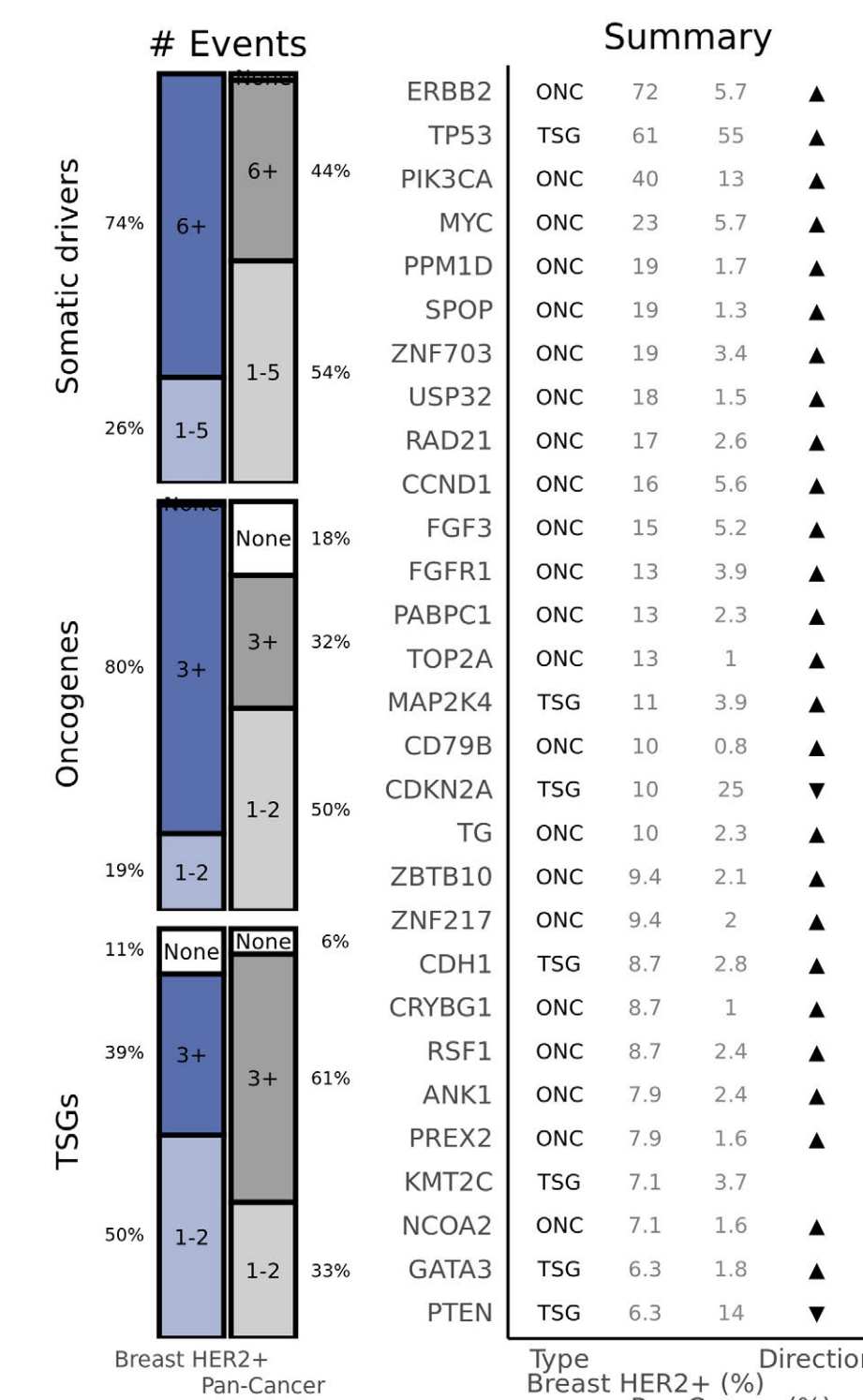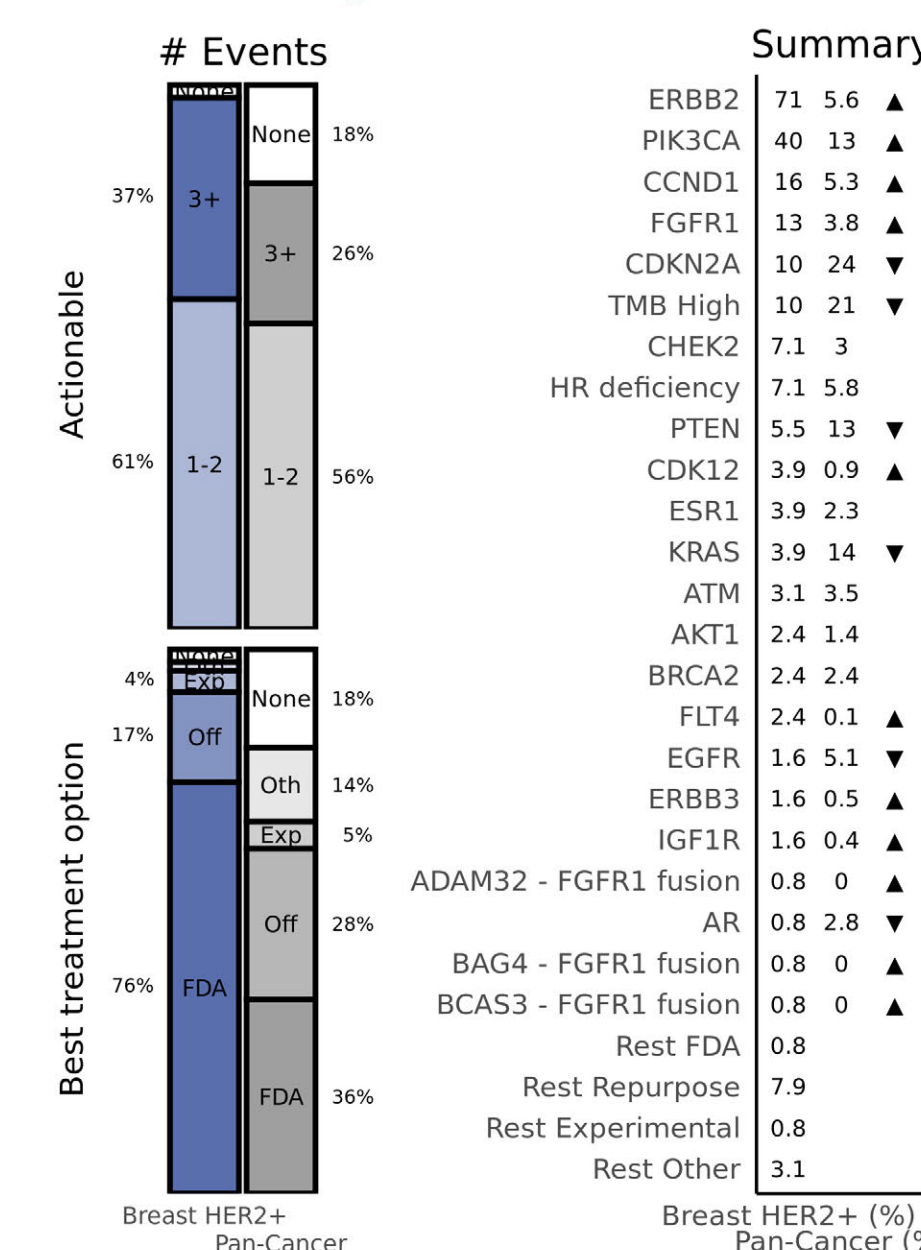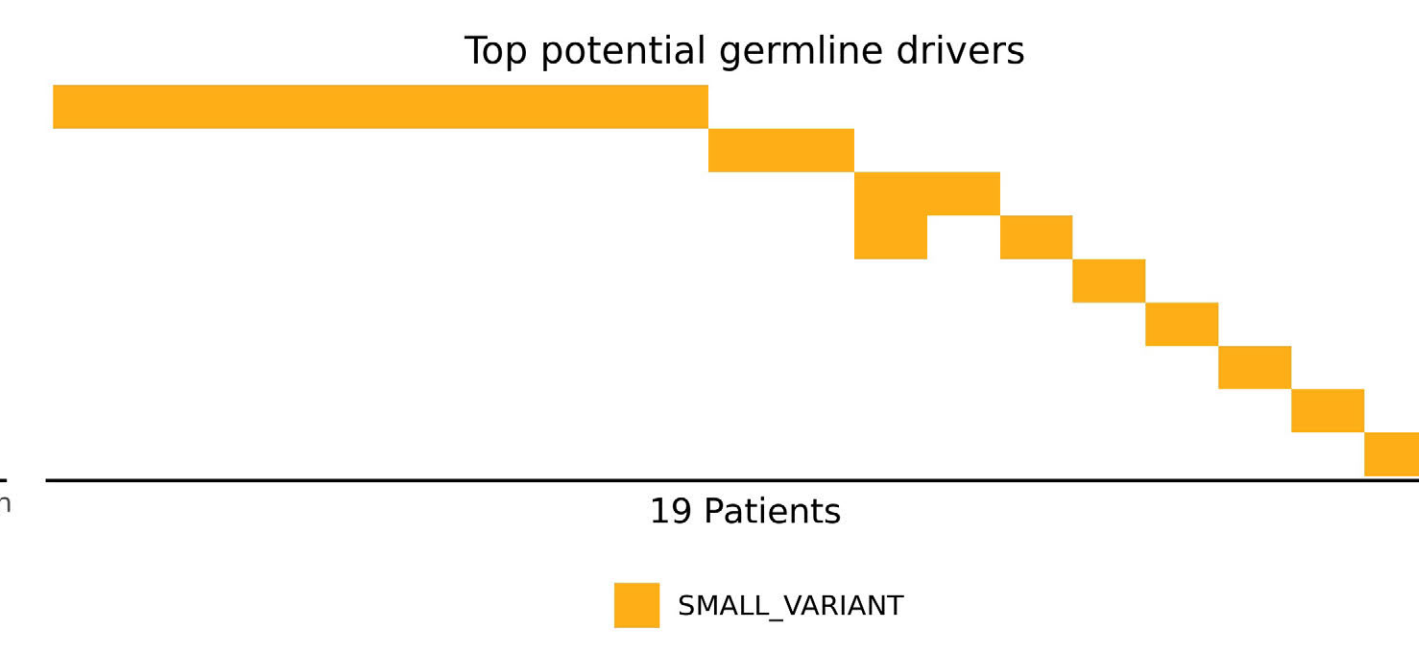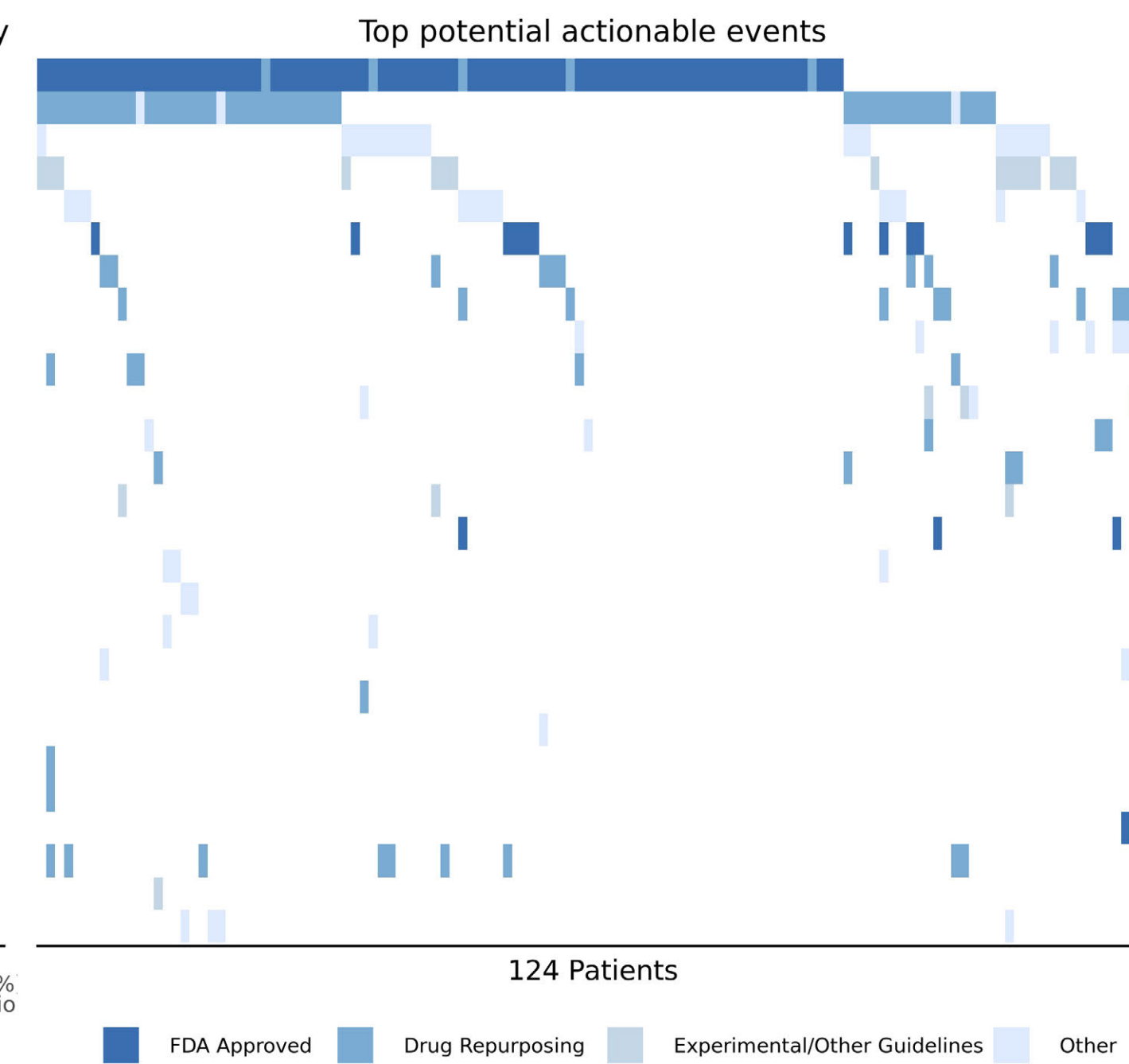** See documentation for further details on the WGS vs Panel coverage study.

Acronym: HER2+
DOIDs included: 60079, 60075, 60076, 1612
Date created from database: 2024-07-06

# The Genomic And Actionability Landscape Of Triple-Negative Breast Cancer

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 157 |
| RNASeq | 75 |
| Age, Sex | 80 |
| Biopsy site | 80 |
| Pretreatment | 80 |
| Treatment | 72 → |
| Response | 60 → |

### Patients with treatment and response data

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 60 | 21 (35%) |
| Multiple | 3 | 2 (67%) |
| Targeted | 0 | 0 |
| Hormonal | 1 | 0 |
| Immuno | 0 | 0 |
| Radio | 11 | 6 (55%) |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

■ Breast TNBC  ■ Pan-Cancer

| | Breast TNBC | Pan-Cancer |
|---|---|---|
| TMB High | 7% | 21% |
| MSI High | 1% | 2% |
| WGD | 71% | 56% |
| Diploid Proportion | 17% | 34% |
| GIE HLA LOH | 21% | 19% |
| GIE Overall | 34% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 32% | 6% |

## Mutational Landscape

### Tumor purity
54% / 55%

### Clonal mutation fraction
93% / 95%

### Tumor mutational burden
3.6 / 4.2 — High 7% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 9,267 | 983 / 940 / 183 | 385 | 92 / 86 |

Number of variants — Quantile

### Telomere Length
0.82 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
8 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.13 / 0.15 — Instable 1% / 2%
MS indels per megabase

### Mean genome ploidy
2.9 / 2.6

### Aneuploidy Score
17 / 16

### % Copy number alteration
60% / 54%

### % Genome LOH
42% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| DNA damage repair: | 23% |
| APOBEC: | 21% |
| Chemical exposure: | 11% |
| Ageing: | 7% |
| Tobacco: | 2% |
| UV light: | 1% |
| Unknown: | 35% |

Breast TNBC 157 Patients
Pan-Cancer 6790 Patients

Breast

Made with bioRender

## Copy Number Alteration Profile

Genes labeled: ADAM30, HOXD9, MCL1, RUNX1, PVRL, CCNE1, STK11, BRCA1, MAP2K4, NF1, ANKRD11, CREBBP, TCF12, RAD51B, RB1, CHD4, FGF3, CCND1, CD44, CDKN2A, ORM2L, SMAD1, PABPC1, PTEN, CRYBG1, CTNNA1, PIK3R1, CCSER1, BAP1, KDM6A
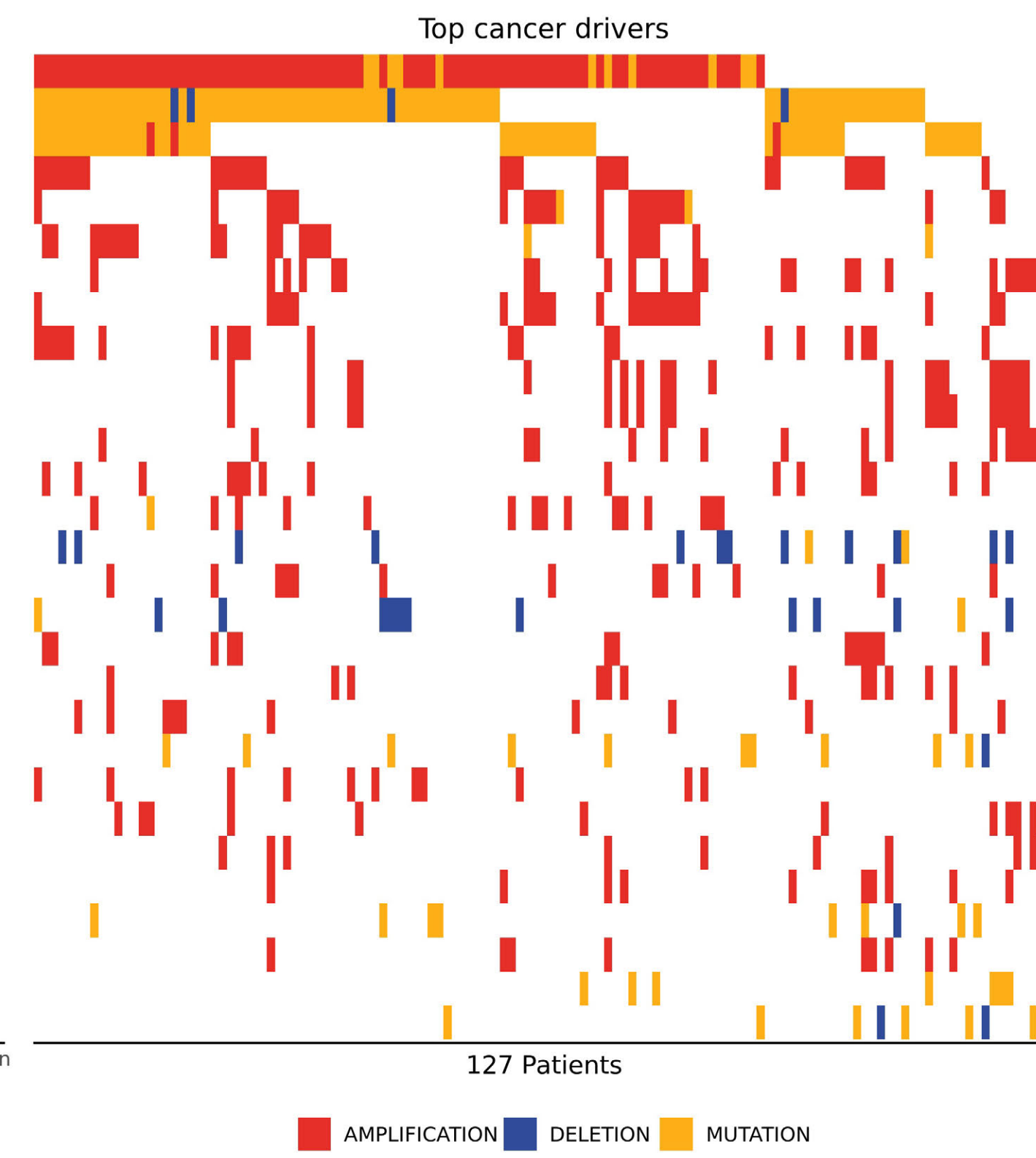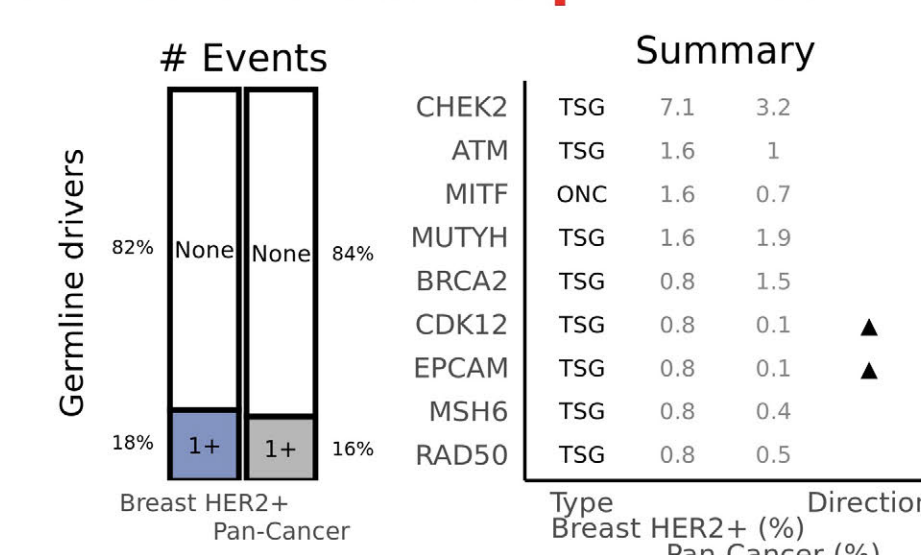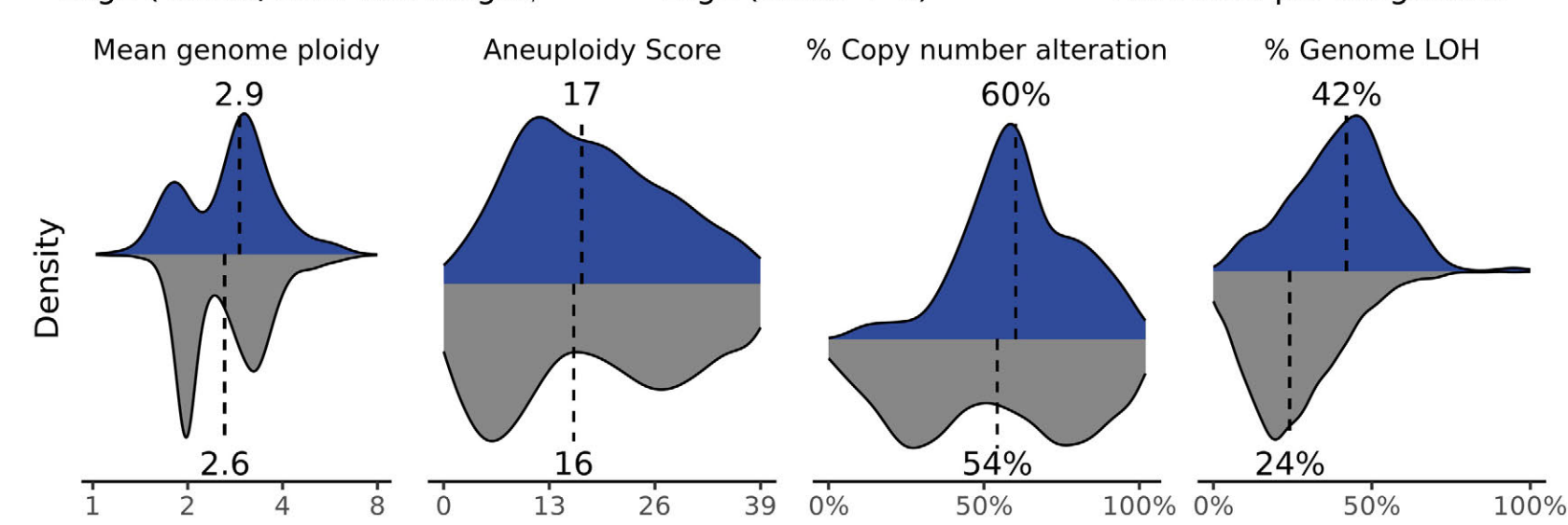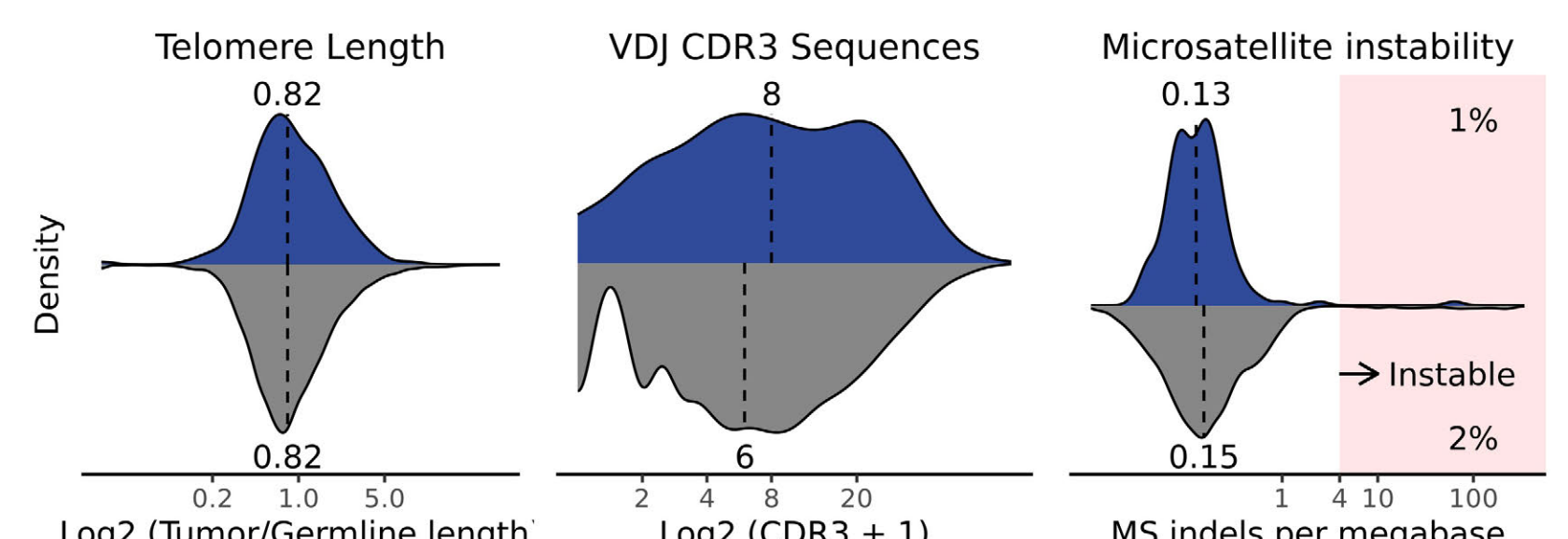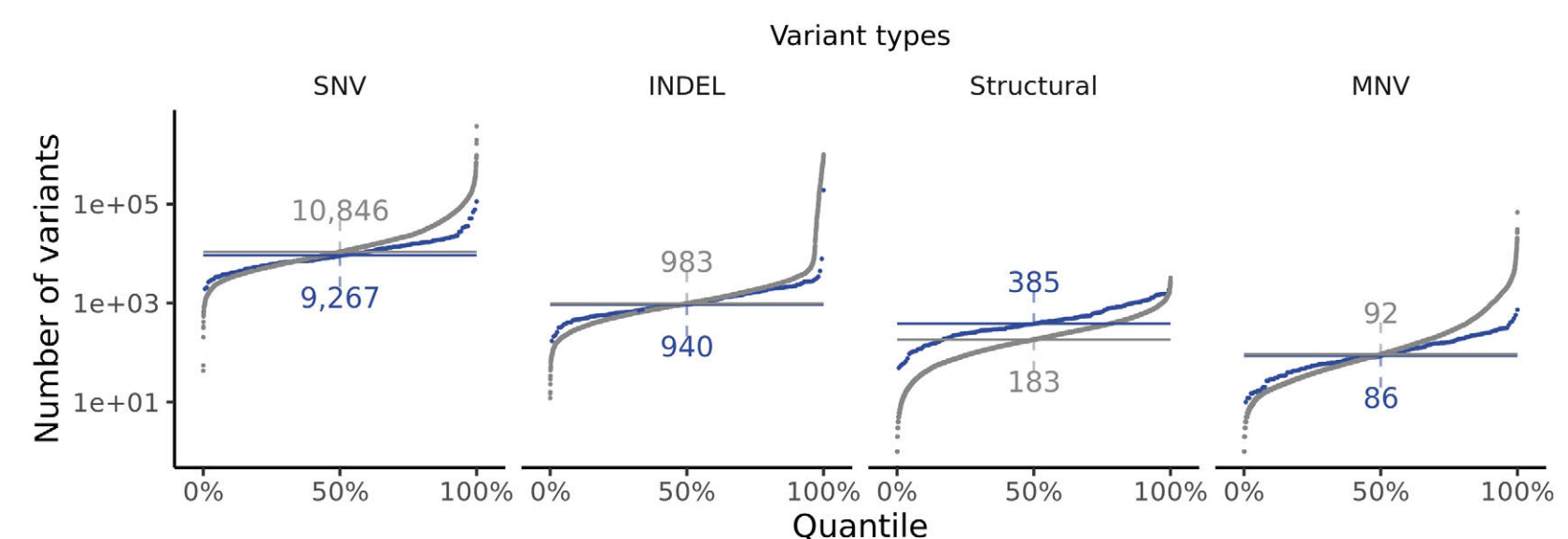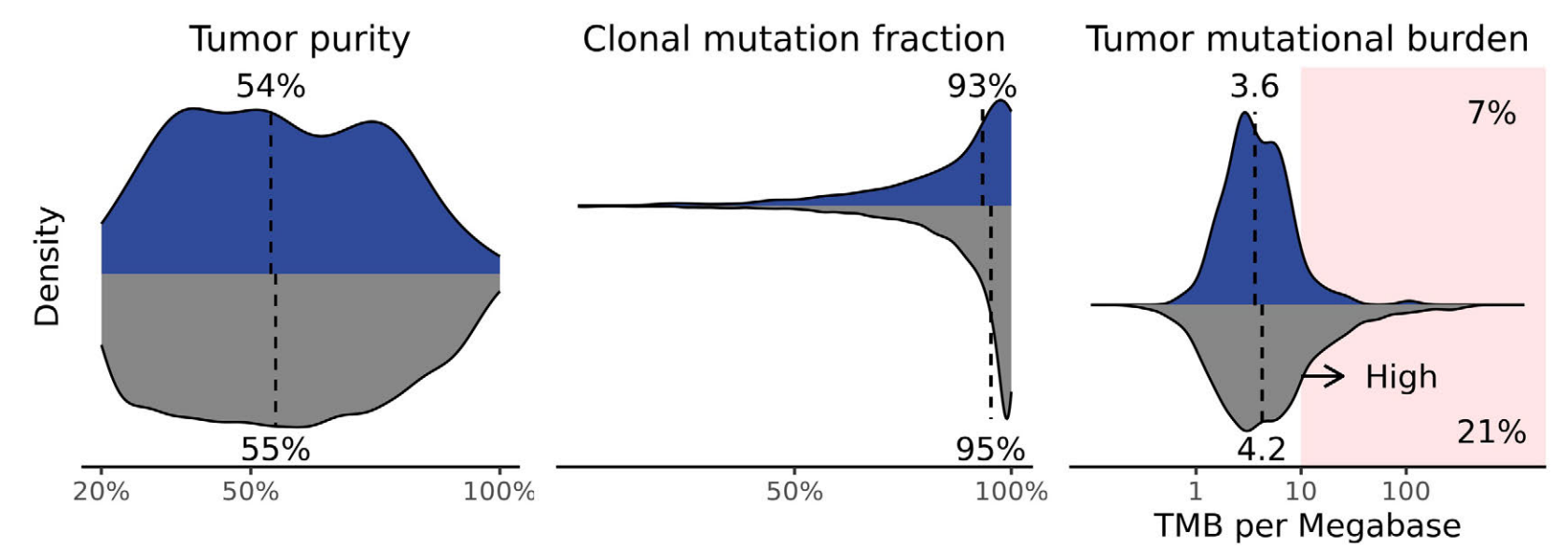
## Cancer Driver Landscape

### # Events / Summary

| | Type | Breast TNBC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 93 | 55 | ▲ |
| RB1 | TSG | 23 | 11 | ▲ |
| PTEN | TSG | 18 | 14 | |
| MYC | ONC | 17 | 5.7 | ▲ |
| CDKN2A | TSG | 13 | 25 | ▼ |
| PIK3CA | ONC | 13 | 13 | |
| CCND1 | ONC | 9.6 | 5.6 | |
| FGF3 | ONC | 9.6 | 5.2 | |
| ADAM30 | TSG | 8.9 | 0.7 | ▲ |
| CSMD1 | TSG | 8.3 | 1.6 | |
| PABPC1 | ONC | 8.3 | 2.3 | ▲ |
| CRYBG1 | TSG | 7.6 | 1 | |
| NF1 | TSG | 7.6 | 5 | |
| CCNE1 | ONC | 7 | 2.4 | |
| KMT2C | TSG | 7 | 3.7 | |
| FGFR1 | ONC | 6.4 | 3.9 | |
| NCOA2 | ONC | 6.4 | 1.6 | ▲ |
| RAD21 | ONC | 6.4 | 2.6 | |
| ANK1 | TSG | 5.7 | 2.4 | |
| CDH1 | TSG | 5.7 | 2.8 | |
| CHD4 | ONC | 5.7 | 1.2 | ▲ |
| KDM6A | TSG | 5.7 | 3.7 | |
| TG | ONC | 5.7 | 2.3 | |
| CD44 | ONC | 5.1 | 1 | ▲ |
| H3C13 | TSG | 5.1 | 0.9 | ▲ |
| MAP2K4 | TSG | 5.1 | 3.9 | |
| MCL1 | TSG | 5.1 | 1.6 | |
| PBRM1 | TSG | 5.1 | 3.2 | |
| PIK3R1 | TSG | 5.1 | 1.7 | |

Somatic drivers: 59% 6+ / 6+ 44%; 41% 1-5 / 1-5 54%
Oncogenes: 19% None / None 18%; 47% 3+ / 3+ 32%; 34% 1-2 / 1-2 50%
TSGs: 69% 3+ / 3+ 61%; 30% 1-2 / 1-2 33%; None

157 Patients

■ AMPLIFICATION  ■ DELETION  ■ MUTATION

## Potentially Actionable Events

### # Events / Summary

| | Breast TNBC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| HR deficiency | 30 | 5.8 | ▲ |
| PTEN | 17 | 13 | |
| CDKN2A | 13 | 24 | ▼ |
| PIK3CA | 12 | 13 | |
| CCND1 | 8.9 | 5.3 | |
| BRCA1 | 7.6 | 1.3 | ▲ |
| FGFR1 | 6.4 | 3.8 | |
| TMB High | 6.4 | 21 | ▼ |
| KRAS | 3.8 | 14 | ▼ |
| VEGFA | 3.8 | 0.7 | ▲ |
| EGFR | 3.2 | 5.1 | |
| KMT2D | 3.2 | 2.9 | |
| FGFR2 | 2.5 | 1.1 | |
| RAD51B | 2.5 | 0.7 | ▲ |
| ATM | 1.9 | 3.5 | |
| CCNE1 | 1.9 | 2.9 | |
| CD274 | 1.9 | 0.5 | |
| CDK4 | 1.9 | 1.9 | |
| ERBB2 | 1.9 | 5.6 | |
| NF1 | 1.9 | 0.4 | ▲ |
| TSC1 | 1.9 | 1.1 | |
| BARD1 | 1.3 | 0.1 | ▲ |
| BRCA2 | 1.3 | 2.4 | |
| Rest FDA | 1.3 | | |
| Rest Repurpose | 7.6 | | |
| Rest Experimental | 3.2 | | |
| Rest Other | 6.4 | | |

Actionable: 21% None / None 18%; 24% 3+ / 3+ 26%; 55% 1-2 / 1-2 56%
Best treatment option: 21% None / None 18%; 15% Oth / Oth 14%; 13% Exp / Exp 5%; 36% Off / Off 28%; 16% FDA / FDA 36%

124 Patients

■ FDA Approved  ■ Drug Repurposing  ■ Experimental/Other Guidelines  ■ Other

## Germline Predisposition

### # Events / Summary

| | Type | Breast TNBC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRCA1 | TSG | 5.1 | 1.1 | ▲ |
| CHEK2 | TSG | 1.9 | 3.2 | |
| MITF | ONC | 1.9 | 0.7 | |
| BARD1 | TSG | 1.3 | 0.1 | ▲ |
| MUTYH | TSG | 1.3 | 1.9 | |
| BRCA2 | TSG | 0.6 | 1.5 | |
| FANCL | TSG | 0.6 | 0.3 | ▲ |
| MLH1 | TSG | 0.6 | 0.2 | ▲ |
| PTCH1 | TSG | 0.6 | 0.1 | ▲ |

Germline drivers: 84% None / None 84%; 16% 1+ / 1+ 16%

22 Patients

■ STRUCTURAL_VARIANT  ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved  ■ Drug Repurposing  ■ Experimental/Other Guidelines  ■ Other  ■ None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Experimental/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 24 | 55 | 44 | 11 | 23 |
| Comprehensive 521 gene panel | 21 | 22 | 52 | 16 | 46 |
| Targeted 50 gene panel | 22 | 22 | 13 | 99 | |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | Total |
|---|---|---|---|---|
| WGS | 0.61 | 0.76 | 0.35 | 1.9 |
| Comprehensive 521 gene panel | 0.23 | 0.54 | 0.24 | 1.2 |
| Targeted 50 gene panel | 0.5 | | | 0.5 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
| HMZ Disruption | 2 |
| Fusion | 1 |
| Partial CN Loss | 1 |

**Drug Repurposing**
| HRD | 47 |
| Fusion | 7 |
| HMZ Disruption | 3 |
| Partial CN Loss | 3 |

**Experimental/Other Guidelines**
| Partial CN Loss | 21 |
| Fusion | 4 |
| HMZ Disruption | 4 |
| Partial CN Gain | 4 |
| Full CN Gain | 2 |

**Other**
| Partial CN Loss | 12 |
| Small Variant | 2 |
| Full CN Loss | 2 |
| HMZ Disruption | 1 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
| Small Variant | 13 |
| TMB High | 10 |
| HMZ Disruption | 2 |
| Fusion | 1 |
| Partial CN Loss | 1 |

**Drug Repurposing**
| HRD | 47 |
| Small Variant | 10 |
| Fusion | 7 |
| HMZ Disruption | 3 |
| Partial CN Loss | 3 |

**Experimental/Other Guidelines**
| Full CN Gain | 48 |
| Partial CN Loss | 21 |
| Small Variant | 5 |
| Partial CN Gain | 5 |
| Fusion | 4 |

**Other**
| Small Variant | 15 |
| Partial CN Loss | 12 |
| Splice Site | 5 |
| Full CN Gain | 3 |
| Partial CN Loss | 2 |

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Breast Cancer (Other)

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 151 |
| RNASeq | 37 |
| Age, Sex | 40 |
| Biopsy site | 35 |
| Pretreatment | 3 |
| Treatment | 2 |
| Response | 1 |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | | |
|---|---|---|
| Chemo | 1 | 0 |
| Multiple | 0 | 0 |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 0 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: ■ Breast Other ■ Pan-Cancer

| | Breast Other | Pan-Cancer |
|---|---|---|
| TMB High | 15% | 21% |
| MSI High | 2% | 2% |
| WGD | 59% | 56% |
| Diploid Proportion | 29% | 34% |
| GIE HLA LOH | 19% | 19% |
| GIE Overall | 28% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 20% | 6% |

## Mutational Landscape

**Tumor purity** — 58% / 55%
**Clonal mutation fraction** — 95% / 95%
**Tumor mutational burden** — 3.7 (15%) / 4.2 (21%) → High; TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 9,295 | 983 / 850 | 342 / 183 | 92 / 80 |

**Telomere Length** — 0.74 / 0.82; Log2 (Tumor/Germline length)
**VDJ CDR3 Sequences** — 7 / 6; Log2 (CDR3 + 1)
**Microsatellite instability** — 0.11 (2%) / 0.15 (2%) → Instable; MS indels per megabase

**Mean genome ploidy** — 2.8 / 2.6
**Aneuploidy Score** — 15 / 16
**% Copy number alteration** — 56% / 54%
**% Genome LOH** — 24% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| APOBEC | 33% |
| DNA damage repair | 24% |
| Ageing | 7% |
| Chemical exposure | 6% |
| Tobacco | 3% |
| UV light | 1% |
| Unknown | 26% |

**Breast Other** 151 Patients — **Pan-Cancer** 6790 Patients — Breast

Made with bioRender

## Copy Number Alteration Profile

(Circular genome plot, chromosomes 1–22, X, Y)

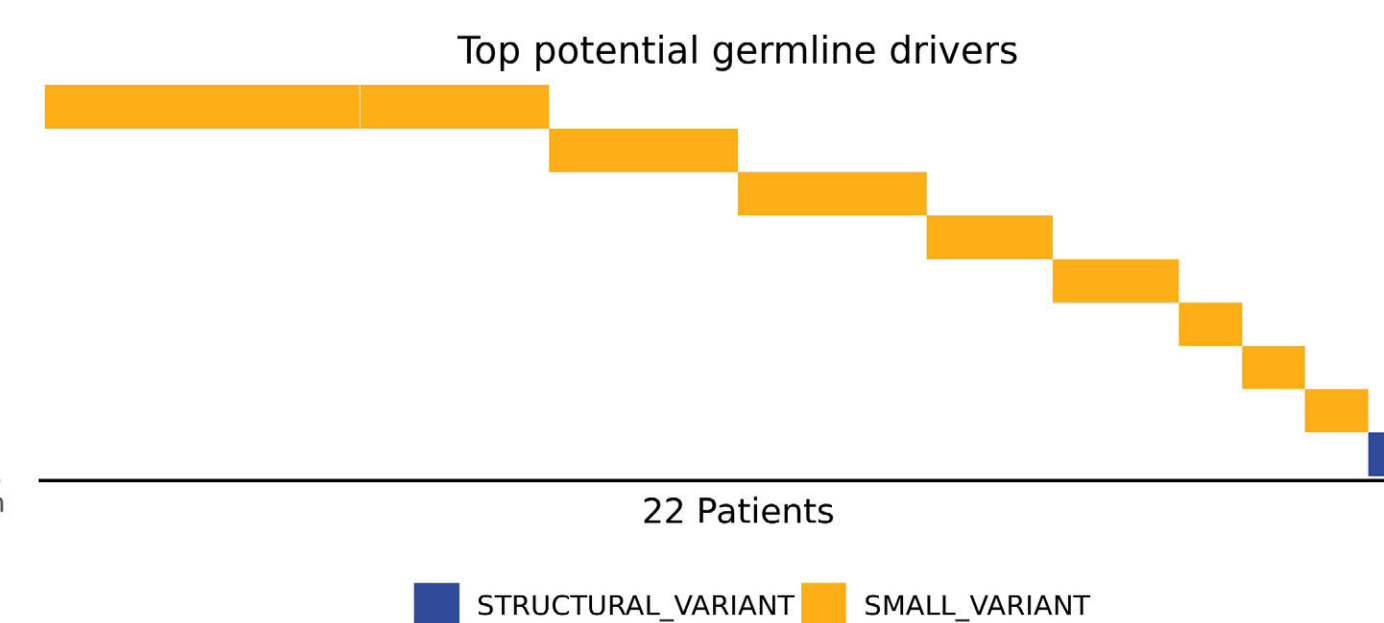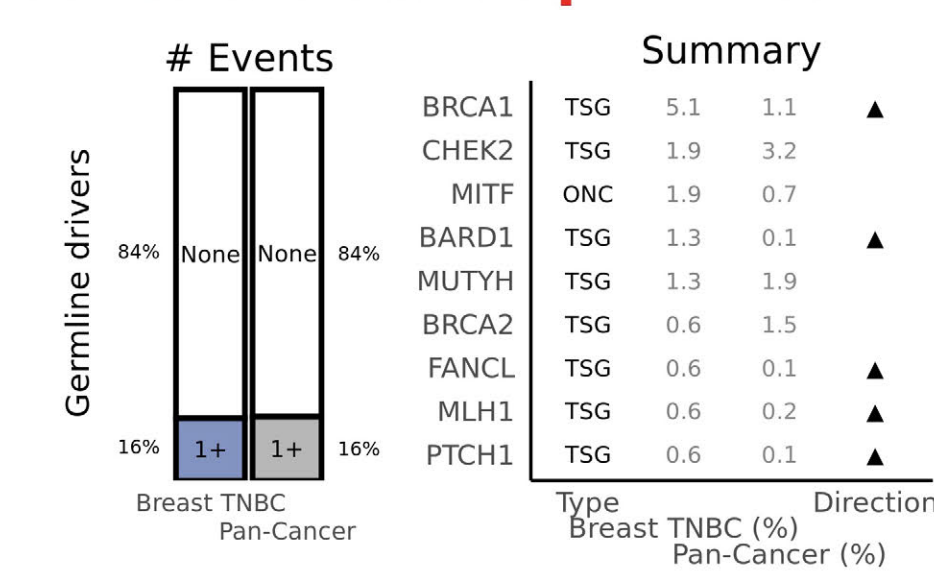Gene labels: CASZ1, LRP1B, FHIT, PIK3R1, CTNNA1, AFDN, KMT7C, IGF1R, ZNF703, MYC, ZMIZ1, CDKN2A, FGFR2, ARID1A, CCND1, RB1, RAD51B, IGF1R, CREBBP, TP53, MAP2K4, NF1, ERBB2, PPM1D, SMARC14, USP3, ZNF217, CCNE1, GMI5

## Cancer Driver Landscape

### # Events / Summary

Somatic drivers: 58% (6+) / 44% (6+); 42% (1-5) / 54% (1-5)
Oncogenes: 54% (3+) / 32% (3+); 33% (1-2) / 50% (1-2)
TSGs: 8% (None) / 18% (None); 56% (3+) / 61% (3+); 36% (1-2) / 33% (1-2)

| Gene | Type | Breast Other (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 60 | 55 | |
| PIK3CA | ONC | 34 | 13 | ▲ |
| PTEN | TSG | 24 | 14 | ▲ |
| CCND1 | ONC | 17 | 5.6 | ▲ |
| ZNF703 | ONC | 15 | 3.4 | ▲ |
| ESR1 | ONC | 14 | 2.7 | ▲ |
| FGFR1 | ONC | 14 | 3.9 | ▲ |
| FGF3 | ONC | 13 | 5.2 | ▲ |
| NF1 | TSG | 13 | 5 | ▲ |
| RB1 | TSG | 12 | 11 | |
| KMT2C | TSG | 11 | 3.7 | ▲ |
| MYC | ONC | 11 | 5.7 | |
| MAP2K4 | TSG | 9.9 | 3.9 | ▲ |
| RSF1 | ONC | 9.9 | 2.4 | ▲ |
| CDH1 | TSG | 9.3 | 2.8 | ▲ |
| MAP3K1 | TSG | 8.6 | 1.5 | ▲ |
| ERBB2 | ONC | 7.9 | 5.7 | |
| ZNF217 | ONC | 7.3 | 2 | |
| CDKN2A | TSG | 6.6 | 25 | ▼ |
| GATA3 | ONC | 6.6 | 1.8 | ▲ |
| ANK1 | TSG | 6 | 2.4 | |
| NCOR1 | TSG | 6 | 1.6 | ▲ |
| CTNNA1 | TSG | 5.3 | 1.8 | ▲ |
| PPM1D | ONC | 5.3 | 1.7 | |
| ZMIZ1 | ONC | 5.3 | 1.3 | ▲ |
| AKT1 | ONC | 4.6 | 1.6 | |
| ARID1A | TSG | 4.6 | 6 | |
| CCNE1 | ONC | 4.6 | 2.4 | |
| FGFR2 | ONC | 4.6 | 1.1 | ▲ |

Top cancer drivers — 148 Patients

Legend: ■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events / Summary

Actionable: 19% (None) / 18% (None); 36% (3+) / 26% (3+); 46% (1-2) / 56% (1-2)
Best treatment option: 19% (None) / 18% (None); 11% (Oth) / 14% (Oth); 7% (Exp) / 5% (Exp); 40% (Off) / 28% (Off); 23% (FDA) / 36% (FDA)

| Gene | Breast Other (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PIK3CA | 30 | 13 | |
| PTEN | 21 | 13 | |
| HR deficiency | 17 | 5.8 | |
| CCND1 | 16 | 5.3 | |
| TMB High | 14 | 21 | |
| FGFR1 | 13 | 3.8 | ▲ |
| ESR1 | 9.9 | 2.3 | ▲ |
| ERBB2 | 7.9 | 5.6 | ▲ |
| CDKN2A | 6 | 24 | ▼ |
| CHEK2 | 5.3 | 3 | |
| FGFR2 | 4.6 | 1.1 | ▲ |
| AKT1 | 4 | 1.4 | |
| BRCA2 | 4 | 2.4 | |
| ATM | 3.3 | 3.5 | |
| BRCA1 | 3.3 | 1.3 | |
| CD274 | 2 | 0.5 | ▲ |
| KRAS | 2 | 14 | ▼ |
| MSI High | 2 | 3.1 | |
| RAD51B | 2 | 0.7 | |
| AR | 1.3 | 2.8 | |
| CDK12 | 1.3 | 0.9 | |
| EGFR | 1.3 | 5.1 | ▼ |
| IGF1R | 1.3 | 0.4 | ▲ |
| Rest Repurpose | 9.9 | | |
| Rest Experimental | 4 | | |
| Rest Other | 6.6 | | |

Top potential actionable events — 123 Patients

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events

Germline drivers: 79% (None) / 84% (None); 21% (1+) / 16% (1+)

| Gene | Type | Breast Other (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 7.3 | 3.2 | |
| BRCA2 | TSG | 3.3 | 1.5 | |
| BRCA1 | TSG | 2 | 1.1 | |
| MUTYH | TSG | 2 | 1.9 | |
| RAD54L | TSG | 1.3 | 0.4 | ▲ |
| SDHA | TSG | 1.3 | 0.5 | |
| ATM | TSG | 0.7 | 1 | |
| CDKN2A | TSG | 0.7 | 0.2 | ▲ |
| MSH6 | TSG | 0.7 | 0.4 | |

Top potential germline drivers — 29 Patients

Legend: ■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other ■ None

### Highest evidence level treatment option identified by test strategy

| Strategy | | | | | | # of patients |
|---|---|---|---|---|---|---|
| WGS | 29 | 68 | 24 | 5 | 25 | |
| Comprehensive 521 gene panel | 27 | 48 | 33 | 6 | 37 | |
| Targeted 50 gene panel | | 52 | 20 | 7 | 69 | |

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.24 | 0.98 | 0.65 | 0.34 | 2.2 |
| Comprehensive 521 gene panel | 0.23 | 0.68 | 0.5 | 0.28 | 1.7 |
| Targeted 50 gene panel | 0.48 | 0.23 | | | 0.8 |

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved:** HMZ Disruption 1; Partial CN Loss 1
**Drug Repurposing:** HRD 26; Fusion 9; Partial CN Loss 8; HMZ Disruption 2
**Experimental/Other Guidelines:** Partial CN Loss 16; Fusion 2; HMZ Disruption 1; Partial CN Gain 2; Full CN Gain 1
**Other:** HMZ Disruption 5; Partial CN Loss 3

### Top missed events by Targeted Panel vs WGS

**FDA Approved:** TMB High 20; Small Variant 9; HMZ Disruption 1; Partial CN Loss 1; Full CN Loss 1
**Drug Repurposing:** Small Variant 28; HRD 26; Fusion 9; Partial CN Loss 8; HMZ Disruption 2
**Experimental/Other Guidelines:** Full CN Gain 35; Partial CN Loss 16; Small Variant 4; Fusion 2; HMZ Disruption 2
**Other:** Small Variant 22; HMZ Disruption 5; Partial CN Loss 3; Full CN Gain 2; Full CN Loss 2

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
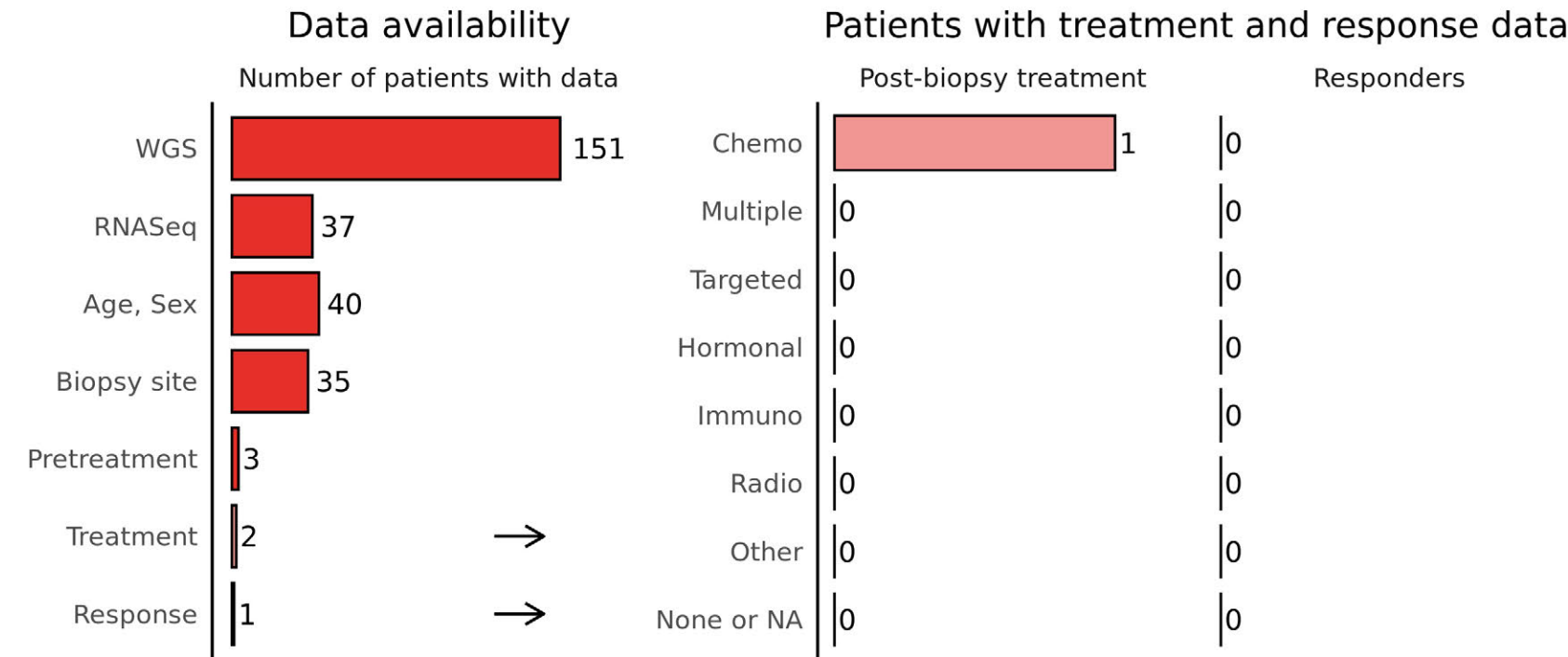Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: BRCA_other
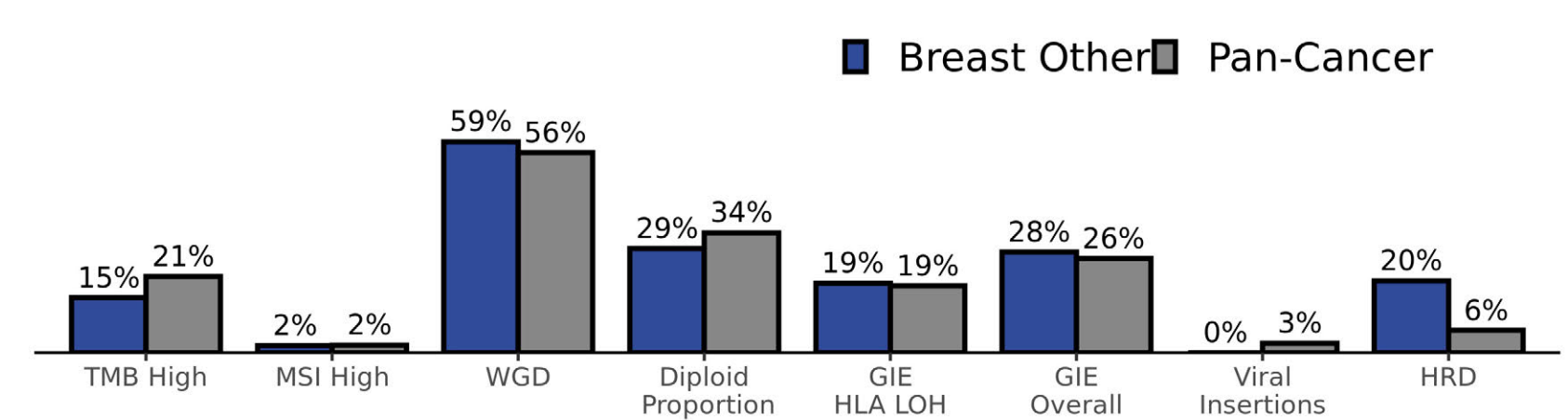DOIDs included: 3459, 1612, 3007, 3458
Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic markers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with: min copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Distruptions, HW inserts, HLA inserts assumed not captured by panels.
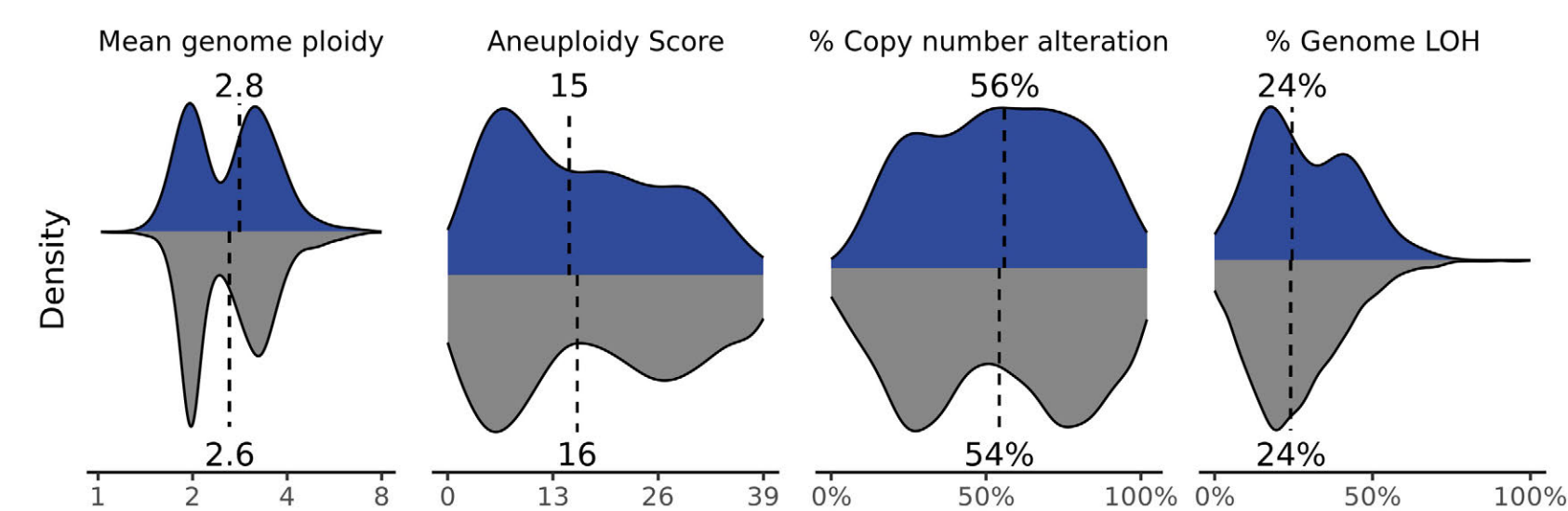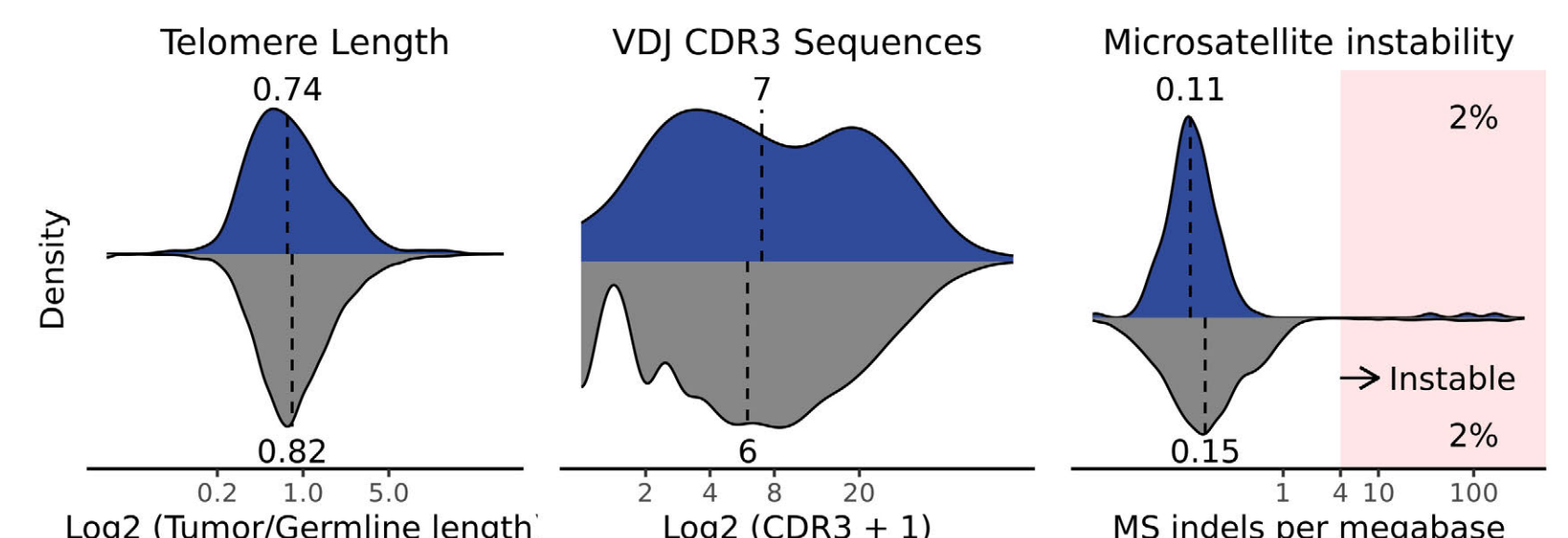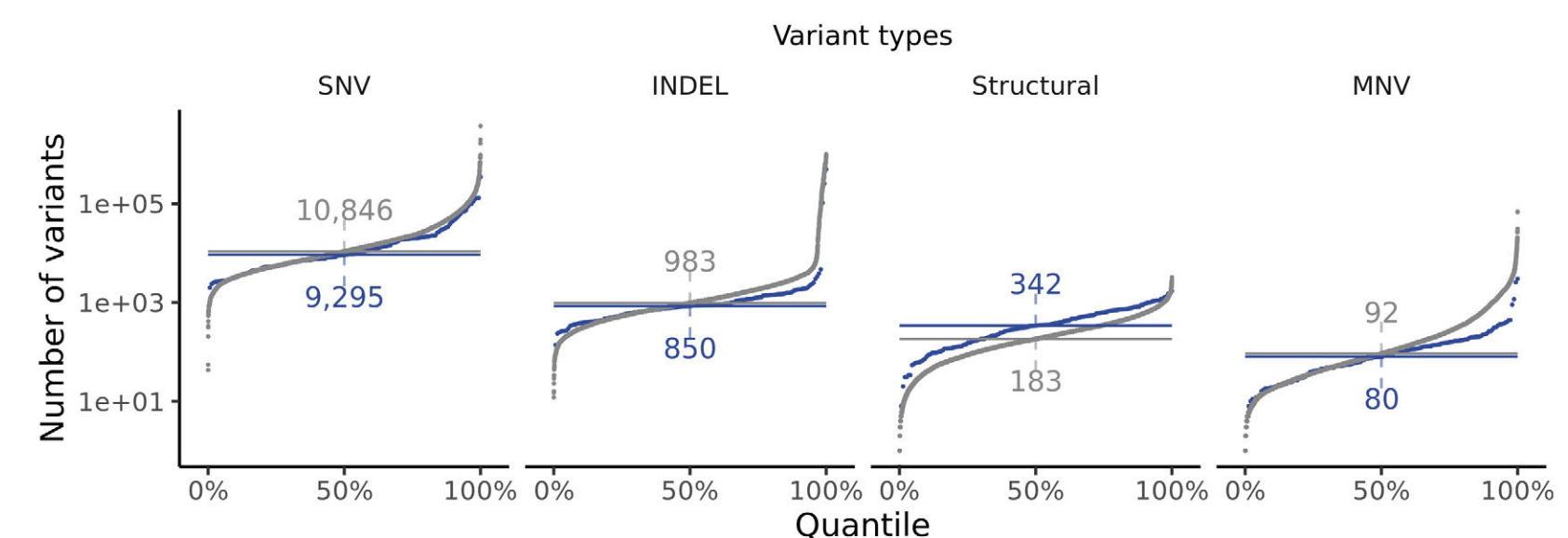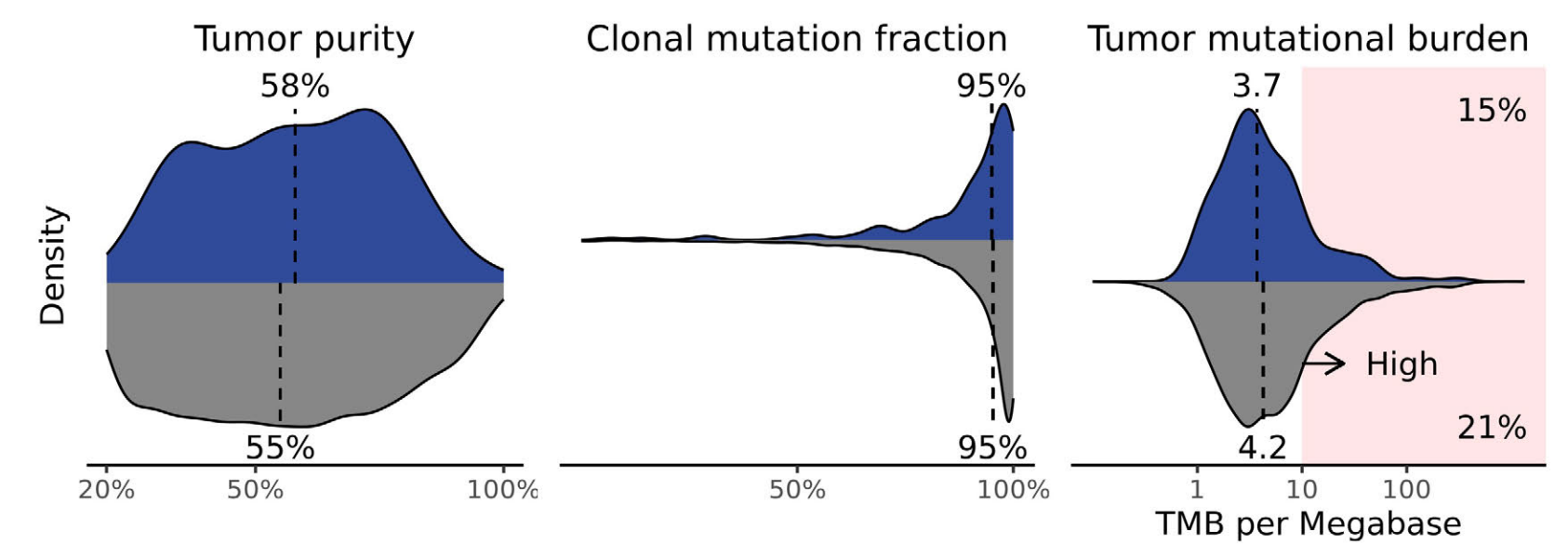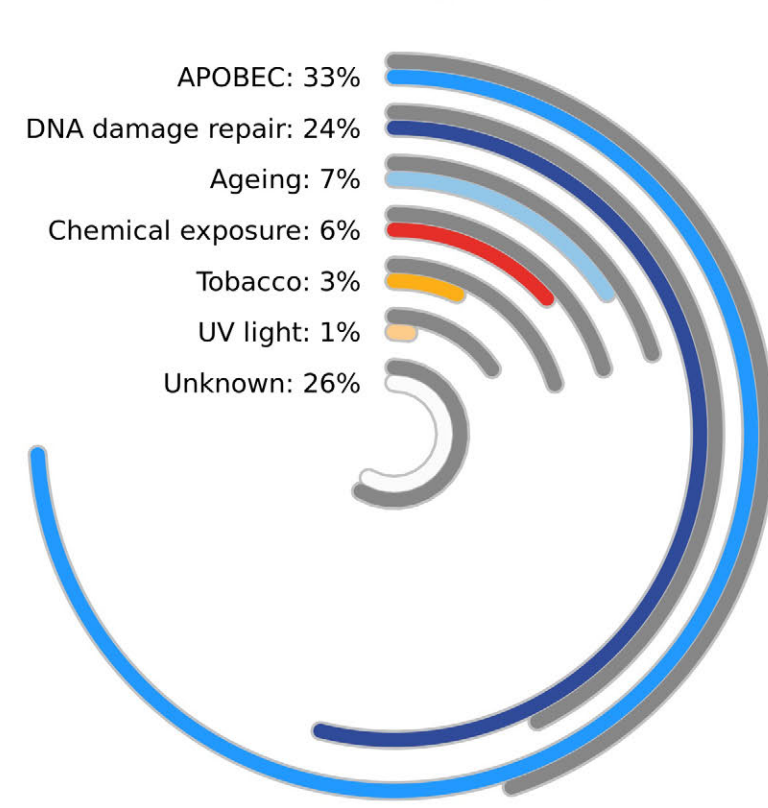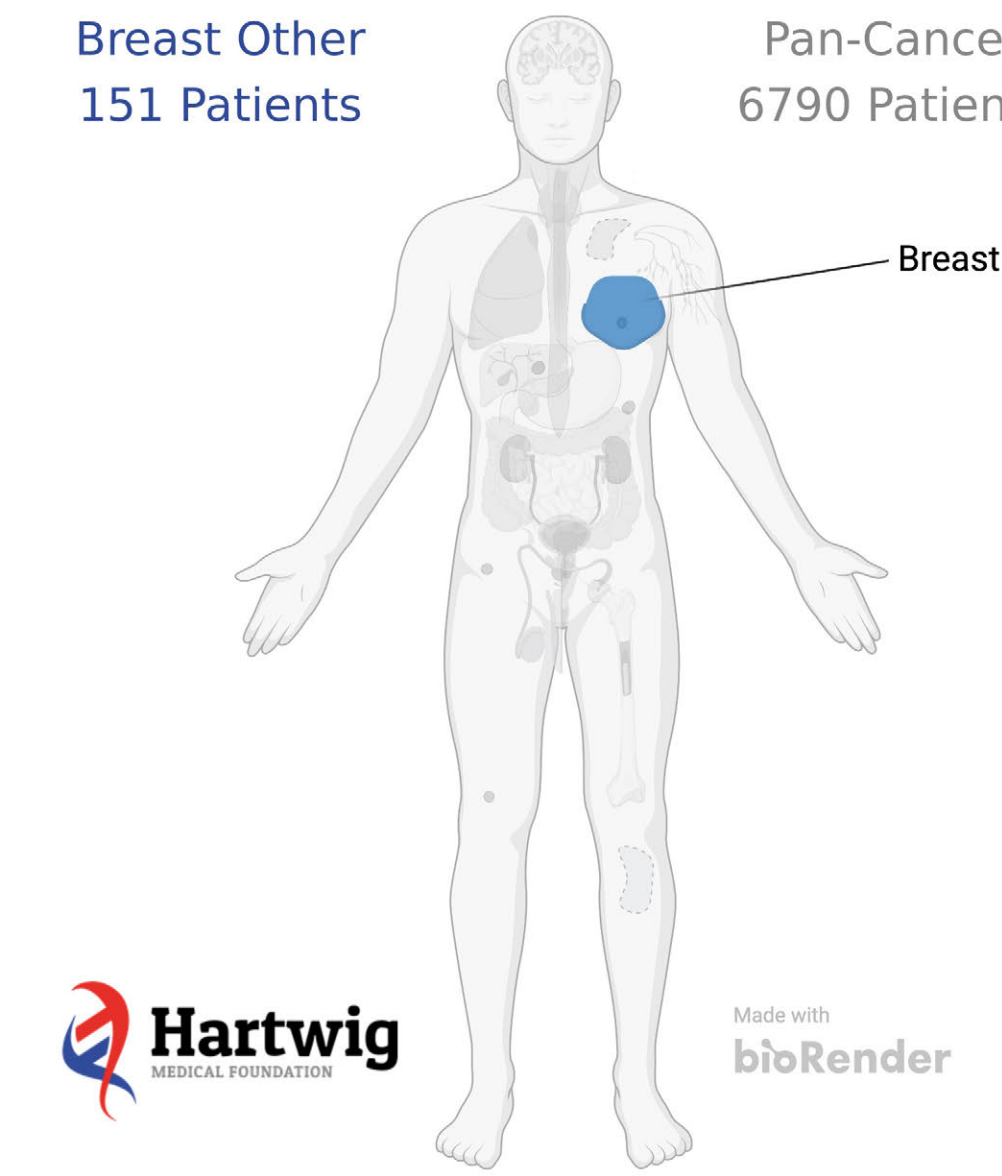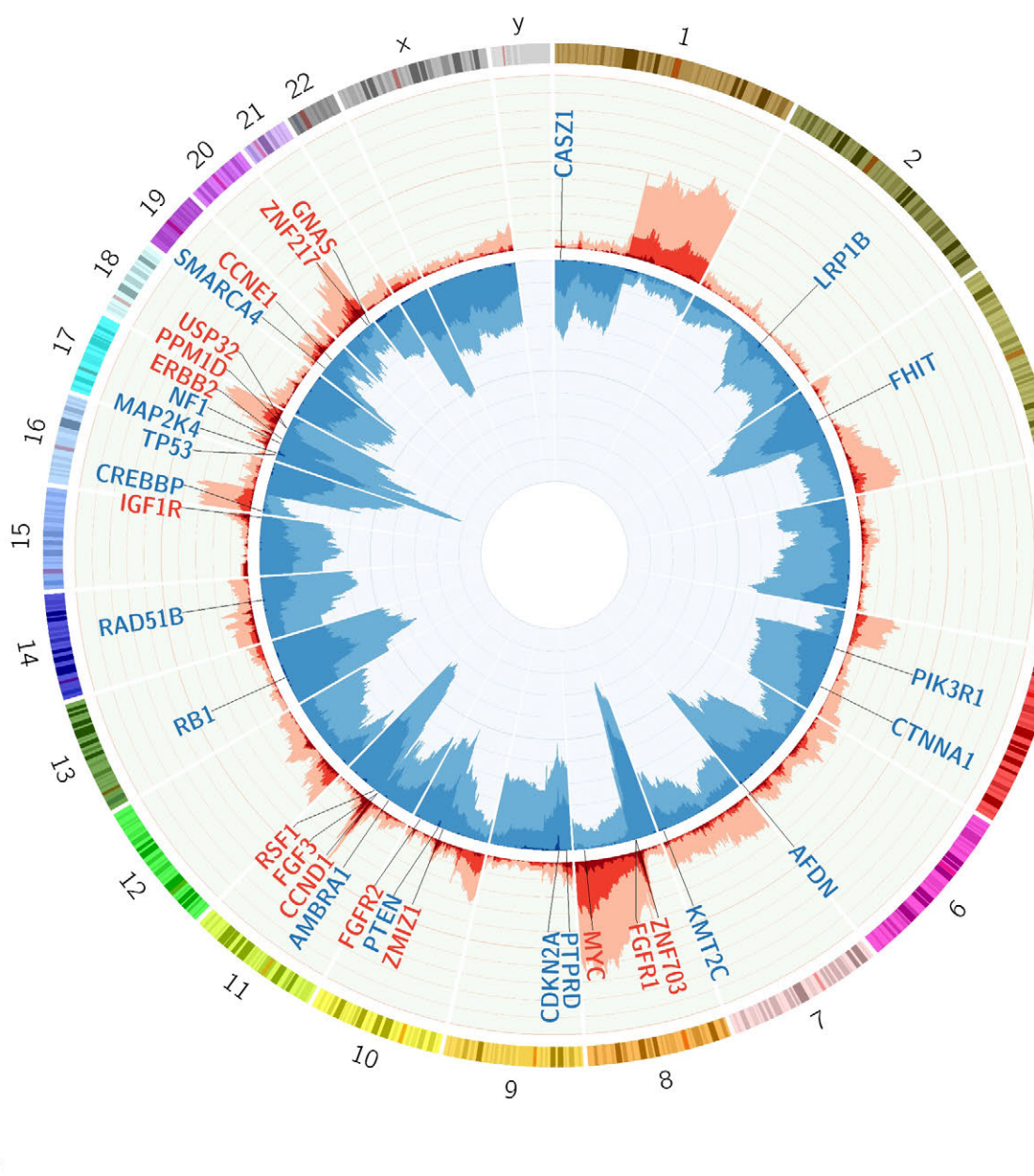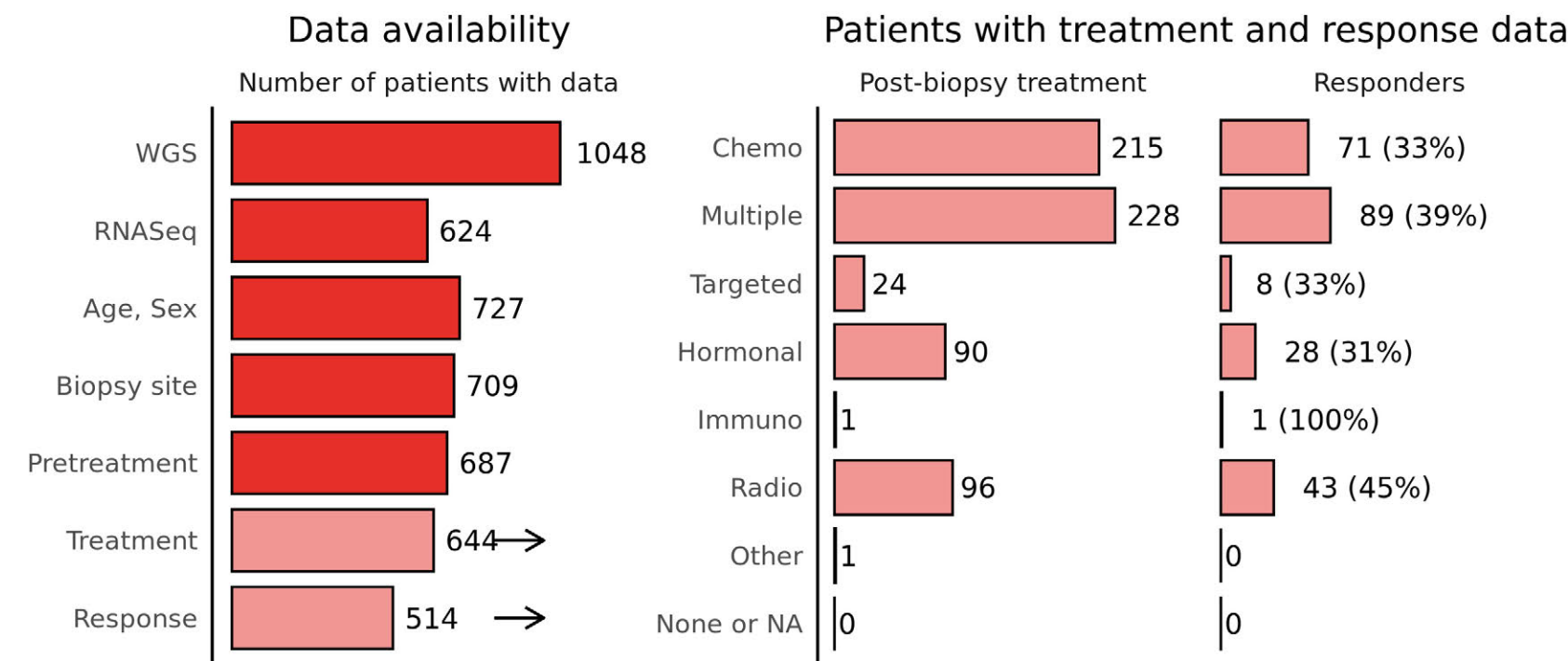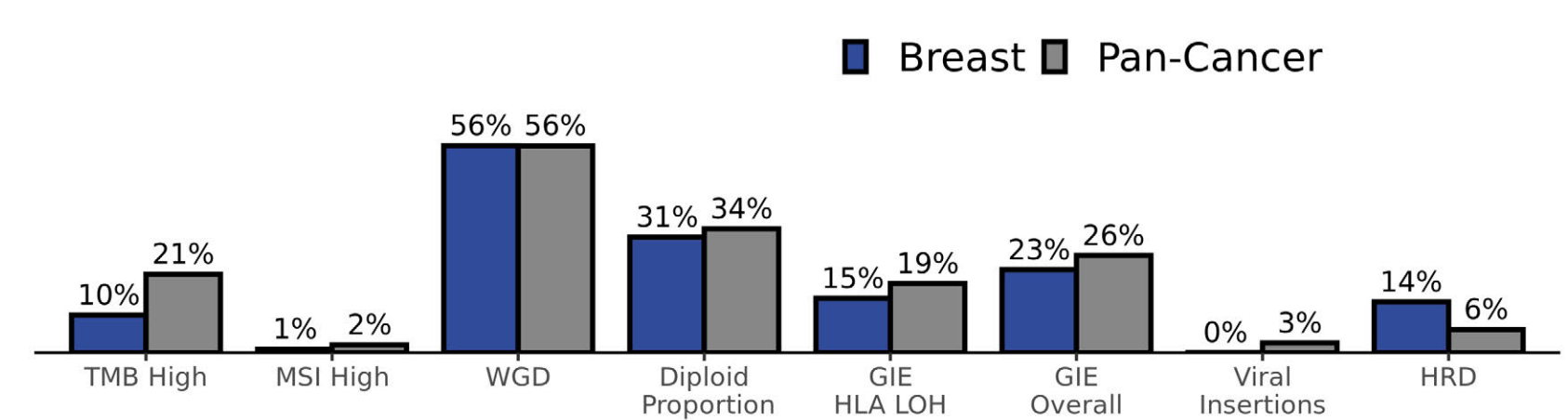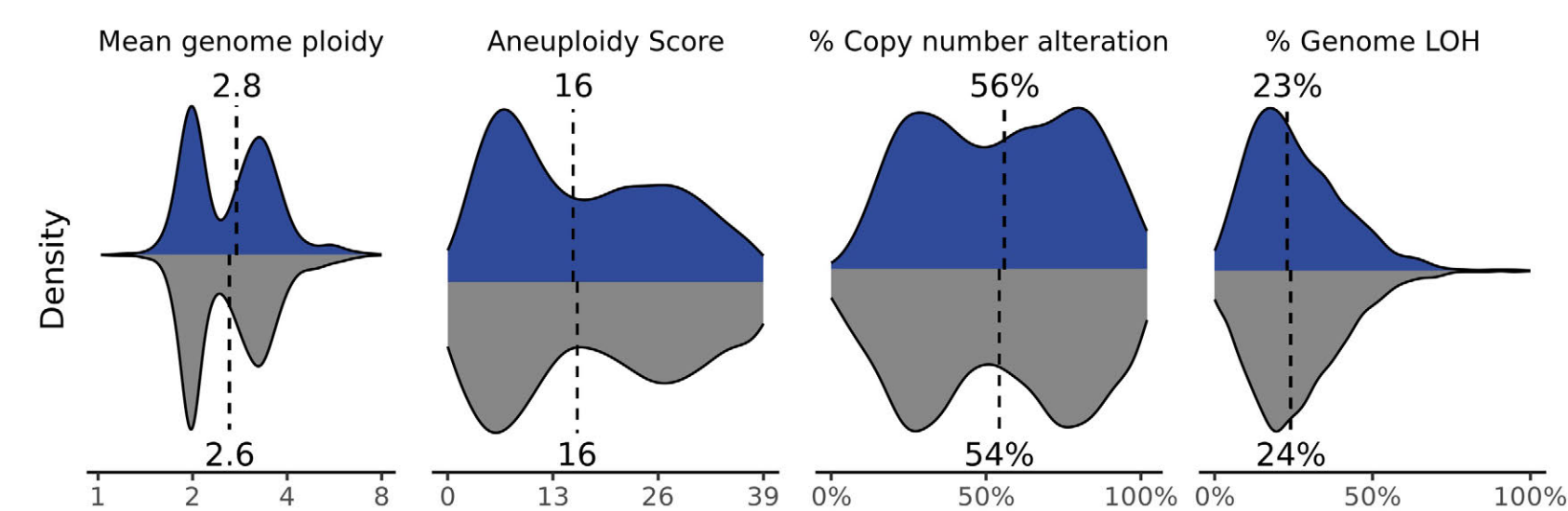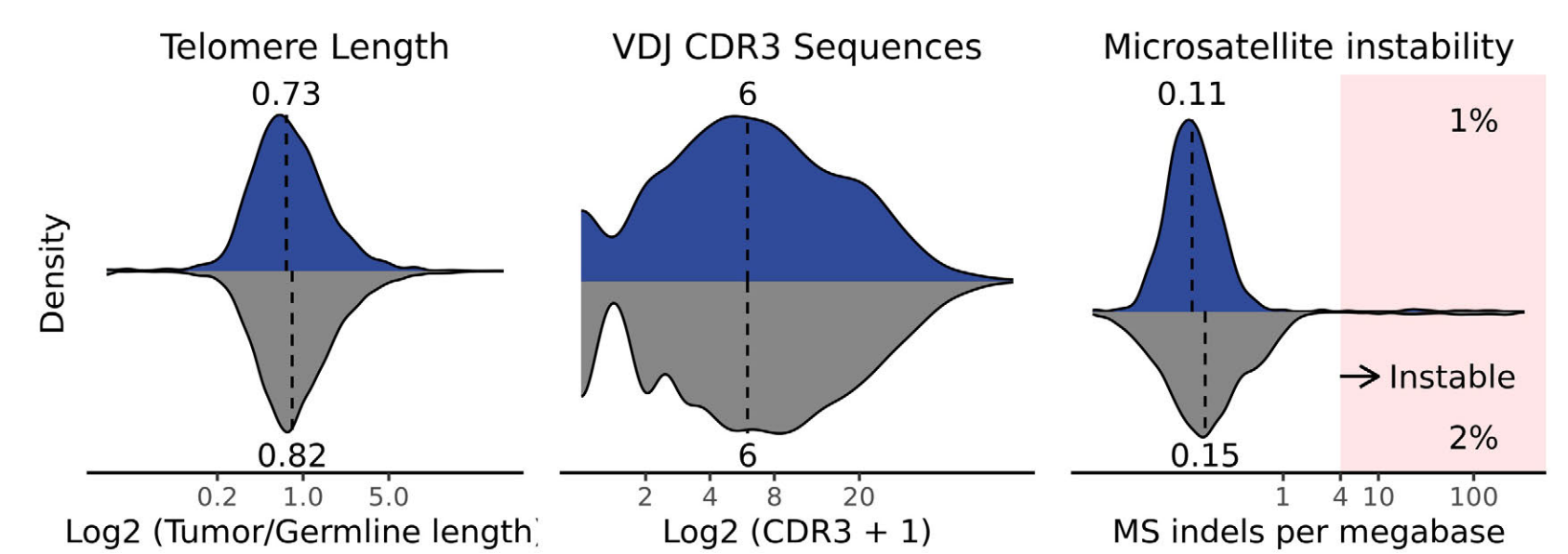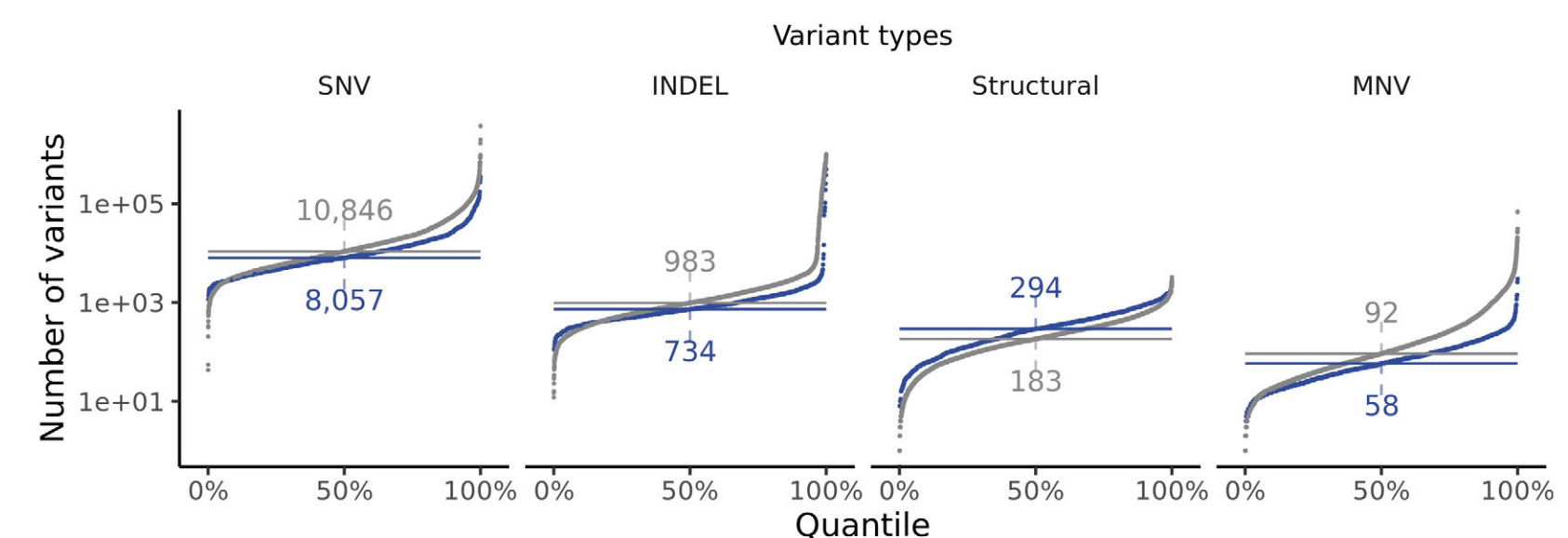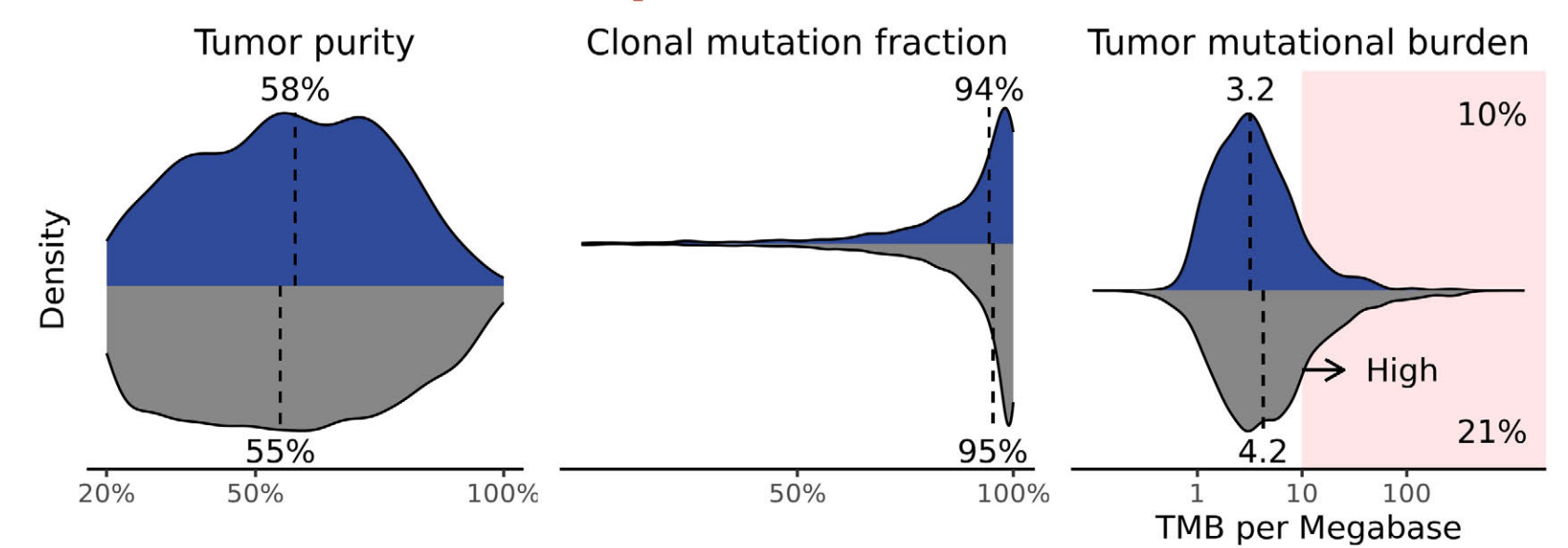** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Breast Cancer

## Cohort Metadata

### Data availability

Number of patients with data

| | |
|---|---|
| WGS | 1048 |
| RNASeq | 624 |
| Age, Sex | 727 |
| Biopsy site | 709 |
| Pretreatment | 687 |
| Treatment | 644 → |
| Response | 514 → |

### Patients with treatment and response data

| Post-biopsy treatment | | Responders | |
|---|---|---|---|
| Chemo | 215 | 71 (33%) |
| Multiple | 228 | 89 (39%) |
| Targeted | 24 | 8 (33%) |
| Hormonal | 90 | 28 (31%) |
| Immuno | 1 | 1 (100%) |
| Radio | 96 | 43 (45%) |
| Other | 1 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Breast / Pan-Cancer

| | TMB High | MSI High | WGD | Diploid Proportion | GIE HLA LOH | GIE Overall | Viral Insertions | HRD |
|---|---|---|---|---|---|---|---|---|
| Breast | 10% | 1% | 56% | 31% | 15% | 23% | 0% | 14% |
| Pan-Cancer | 21% | 2% | 56% | 34% | 19% | 26% | 3% | 6% |

## Mutational Landscape

### Tumor purity
58% / 55%

### Clonal mutation fraction
94% / 95%

### Tumor mutational burden
3.2 / 4.2, High 10% / 21%, TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Breast | 8,057 | 734 | 294 | 58 |
| | 10,846 | 983 | 183 | 92 |

Number of variants — Quantile

### Telomere Length
0.73 / 0.82 — Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
6 / 6 — Log2 (CDR3 + 1)

### Microsatellite instability
0.11 / 0.15, Instable 1% / 2% — MS indels per megabase

### Mean genome ploidy
2.8 / 2.6

### Aneuploidy Score
16 / 16

### % Copy number alteration
56% / 54%

### % Genome LOH
23% / 24%

## Processes Underlying Mutations

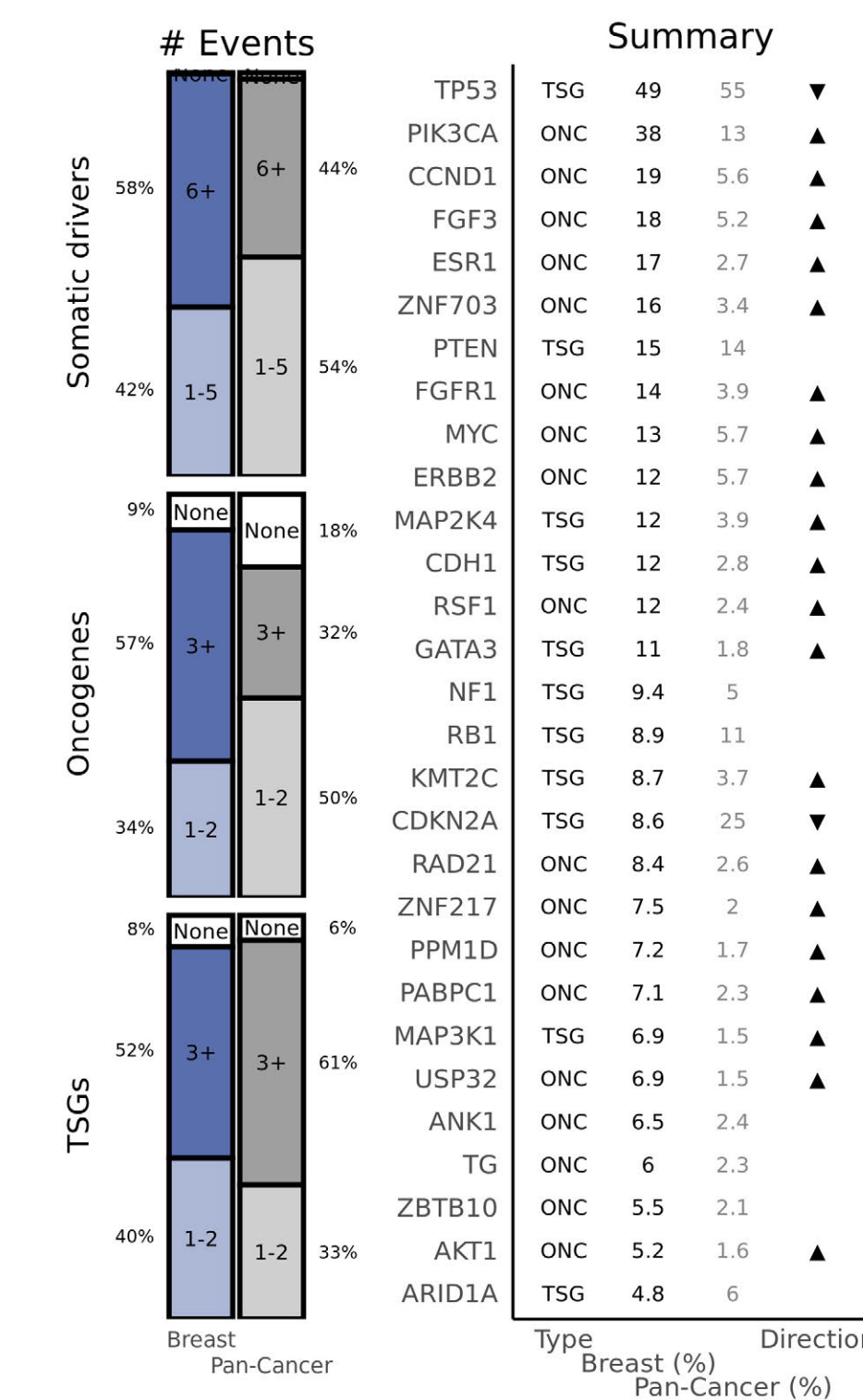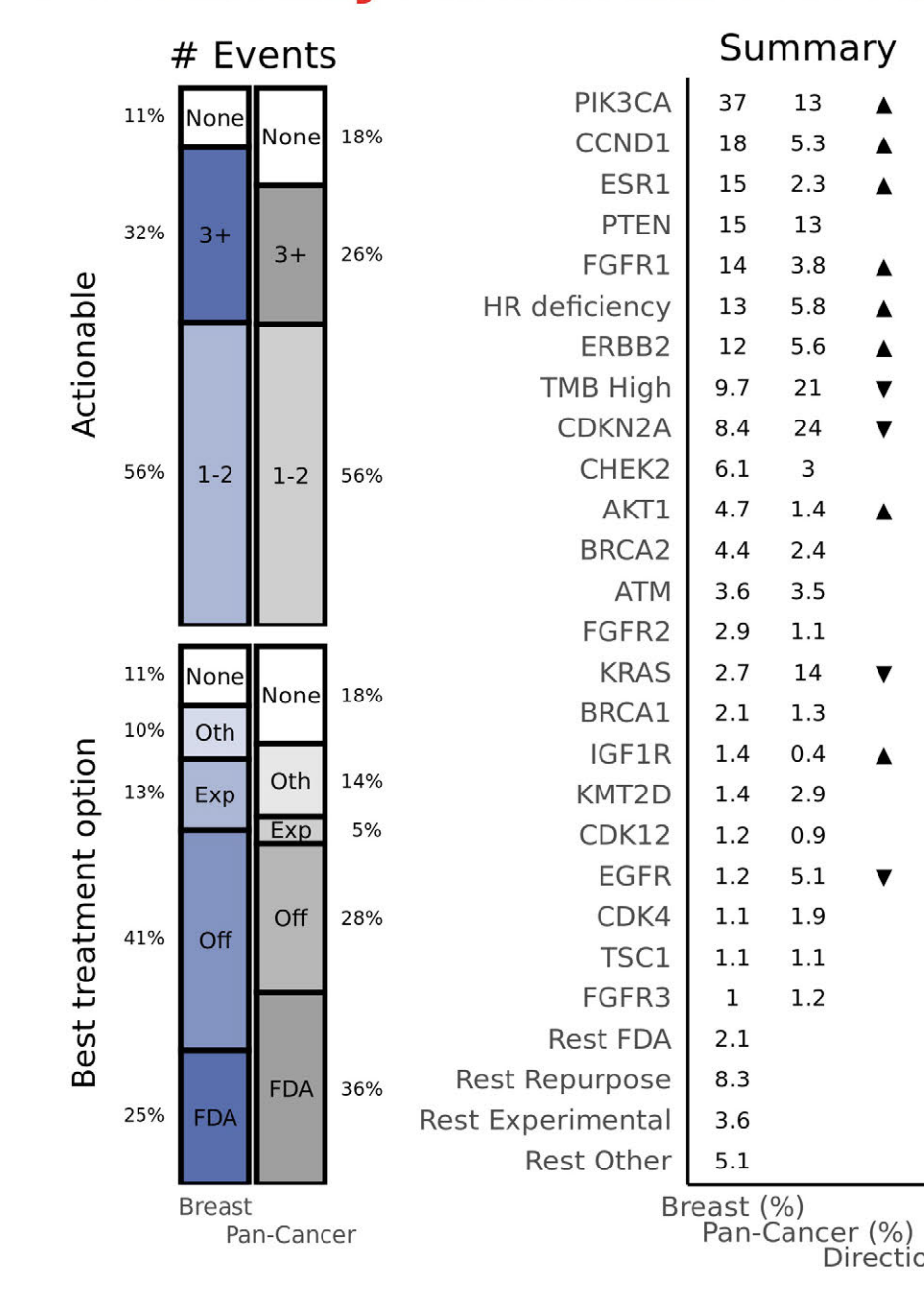| | |
|---|---|
| APOBEC | 39% |
| DNA damage repair | 17% |
| Chemical exposure | 7% |
| Ageing | 7% |
| Tobacco | 2% |
| UV light | 1% |
| Unknown | 27% |

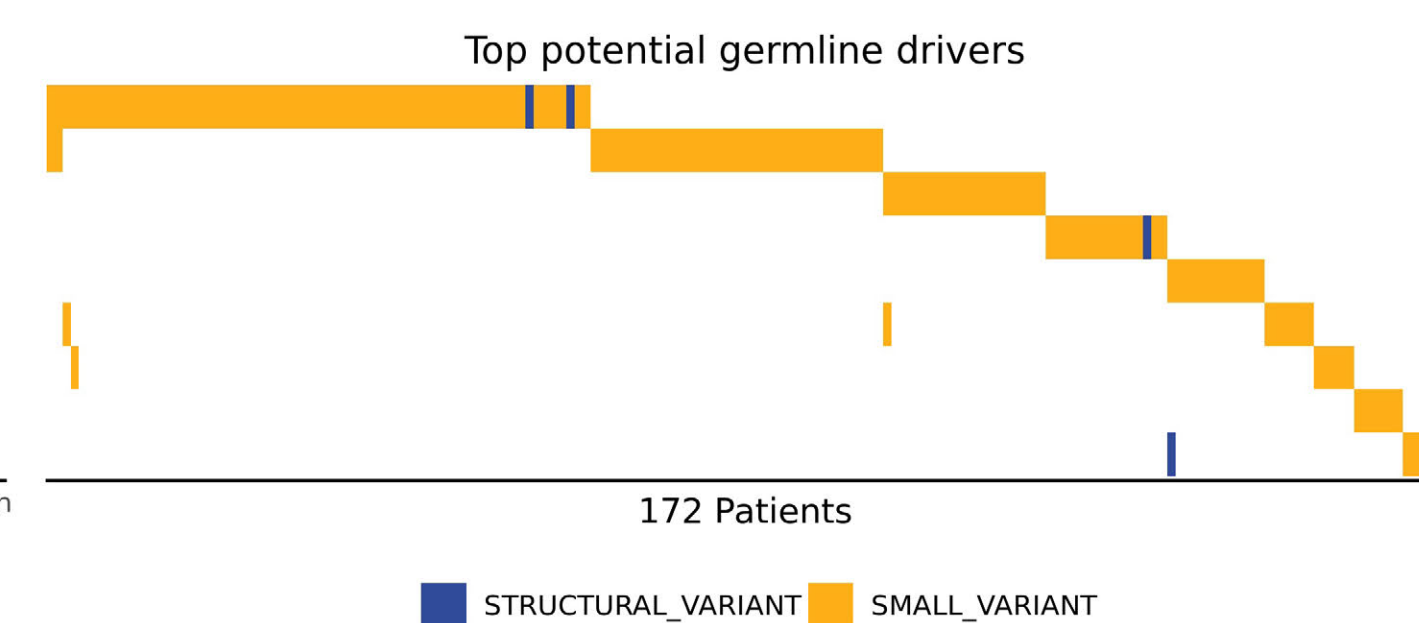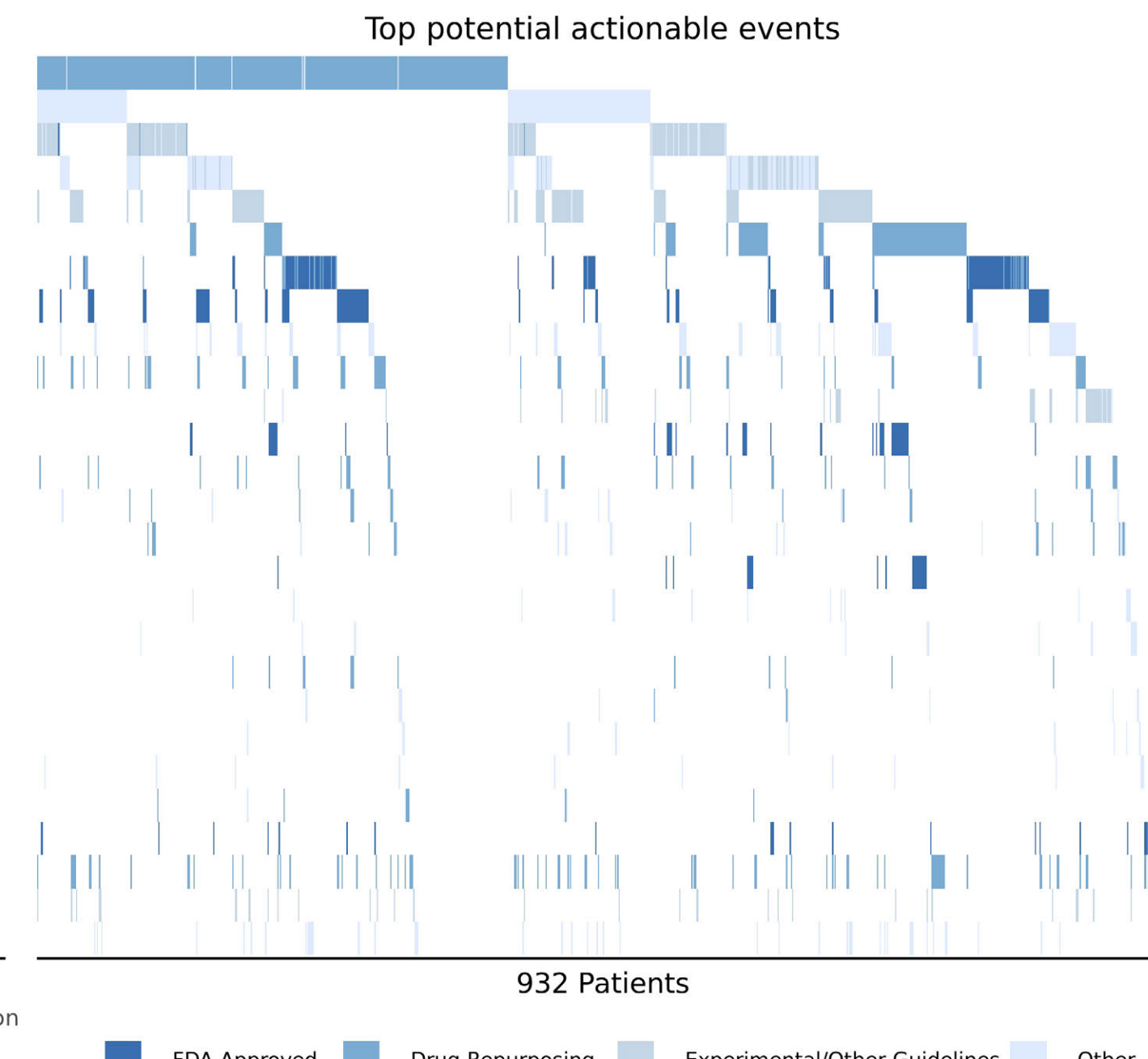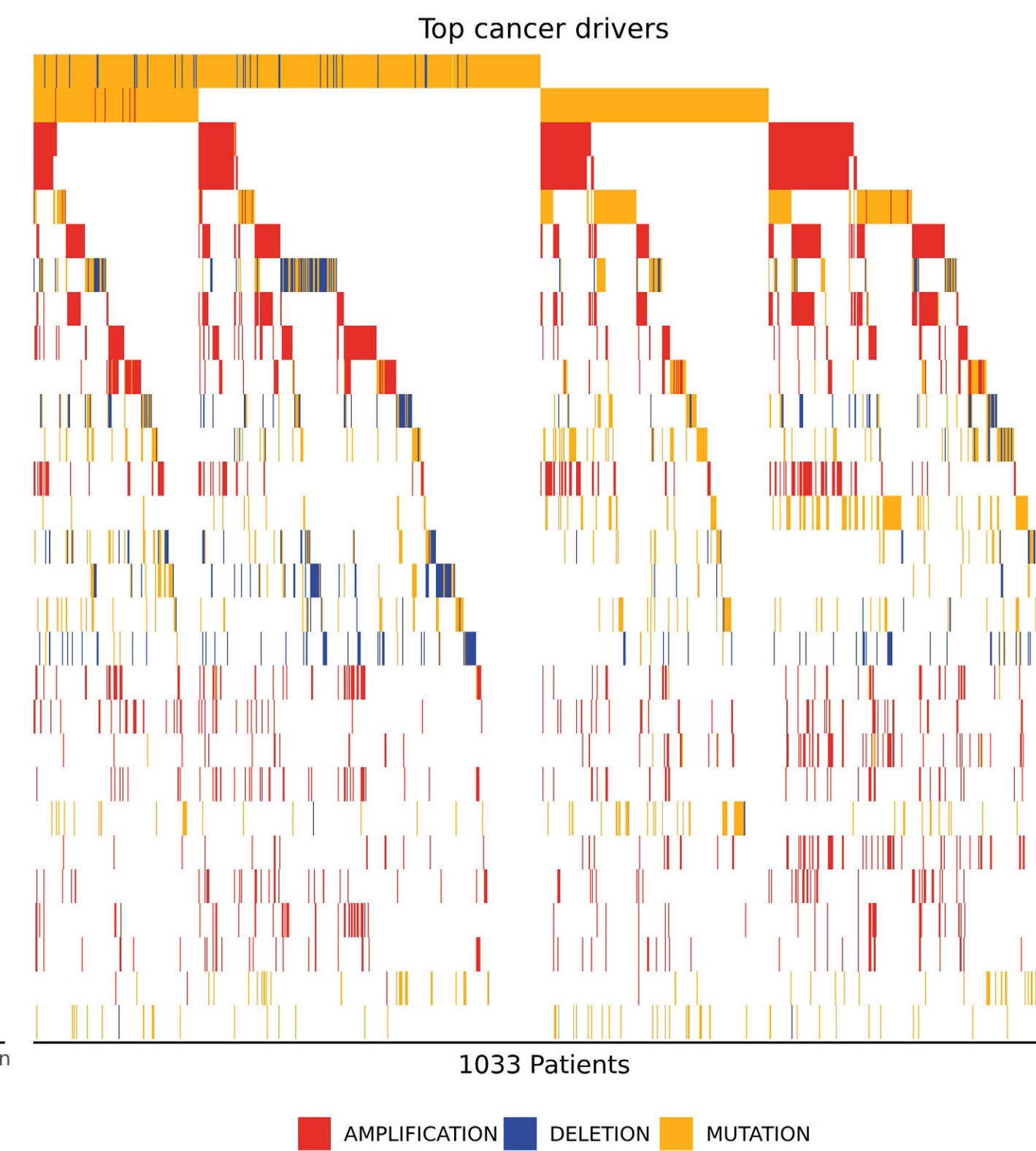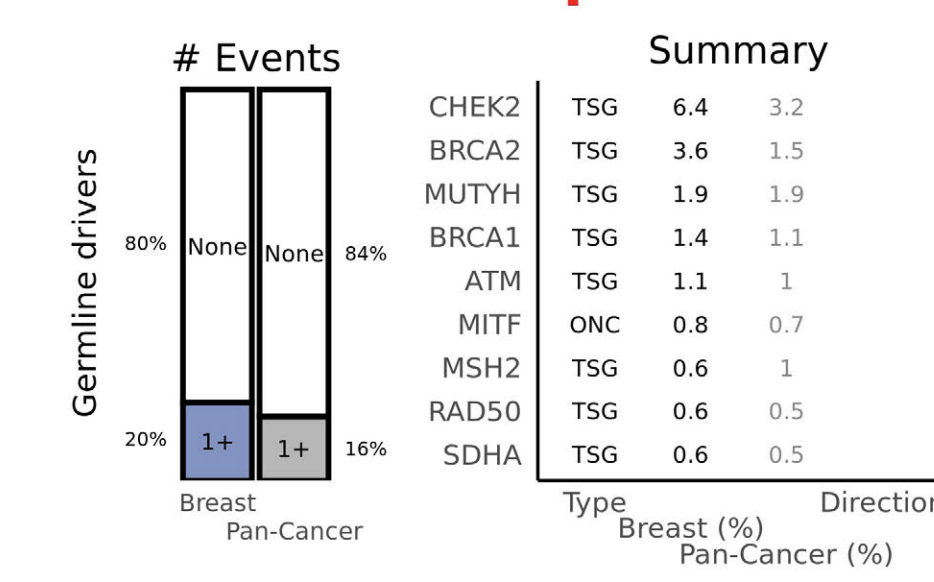Breast 1048 Patients — Pan-Cancer 6790 Patients — Breast

## Copy Number Alteration Profile



## Cancer Driver Landscape

Top cancer drivers — 1033 Patients

| Gene | Type | Breast (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 49 | 55 | ▼ |
| PIK3CA | ONC | 38 | 13 | ▲ |
| CCND1 | ONC | 19 | 5.6 | ▲ |
| FGF3 | ONC | 18 | 5.2 | ▲ |
| ESR1 | ONC | 17 | 2.7 | ▲ |
| ZNF703 | ONC | 16 | 3.4 | ▲ |
| PTEN | TSG | 15 | 14 | |
| FGFR1 | ONC | 14 | 3.9 | ▲ |
| MYC | ONC | 12 | 5.7 | |
| ERBB2 | ONC | 12 | 5.7 | ▲ |
| MAP2K4 | TSG | 12 | 3.9 | ▲ |
| CDH1 | TSG | 12 | 2.8 | ▲ |
| RSF1 | ONC | 12 | 2.4 | ▲ |
| GATA3 | TSG | 11 | 1.8 | ▲ |
| NF1 | TSG | 9.4 | 5 | |
| RB1 | TSG | 8.9 | 11 | |
| KMT2C | TSG | 8.7 | 3.7 | ▲ |
| CDKN2A | TSG | 8.6 | 25 | ▼ |
| RAD21 | ONC | 8.4 | 2.6 | ▲ |
| ZNF217 | ONC | 7.5 | 2 | |
| PPM1D | TSG | 7.2 | 1.7 | ▲ |
| PABPC1 | ONC | 7.1 | 2.3 | ▲ |
| MAP3K1 | ONC | 6.9 | 1.5 | ▲ |
| USP32 | ONC | 6.9 | 1.5 | ▲ |
| ANK1 | ONC | 6.5 | 2.4 | |
| TG | ONC | 6 | 2.3 | |
| ZBTB10 | ONC | 5.5 | 2.1 | |
| AKT1 | ONC | 5.2 | 1.6 | ▲ |
| ARID1A | TSG | 4.8 | 5.1 | |

AMPLIFICATION · DELETION · MUTATION

Somatic drivers: 58% 6+ / 44% 6+ / 42% 1-5 / 1-5
Oncogenes: 9% None / 18% None / 57% 3+ / 32% 3+ / 34% 1-2 / 50% 1-2
TSGs: 8% None / None / 52% 3+ / 61% 3+ / 40% 1-2 / 33% 1-2

## Potentially Actionable Events

Top potential actionable events — 932 Patients

| Gene | Breast (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PIK3CA | 37 | 13 | ▲ |
| CCND1 | 18 | 5.3 | ▲ |
| ESR1 | 15 | 2.3 | ▲ |
| PTEN | 15 | 13 | |
| FGFR1 | 14 | 3.8 | ▲ |
| HR deficiency | 13 | 5.8 | ▲ |
| ERBB2 | 12 | 5.6 | ▲ |
| TMB High | 9.7 | 21 | ▼ |
| CDKN2A | 8.4 | 24 | ▼ |
| CHEK2 | 6.1 | 3 | |
| AKT1 | 4.7 | 1.4 | ▲ |
| BRCA2 | 4.4 | 2.4 | |
| ATM | 3.6 | 3.5 | |
| FGFR2 | 2.9 | 1.1 | |
| KRAS | 2.7 | 14 | ▼ |
| BRCA1 | 2.1 | 1.3 | |
| IGF1R | 1.4 | 0.4 | ▲ |
| KMT2D | 1.4 | 2.9 | |
| CDK12 | 1.2 | 0.9 | |
| EGFR | 1.2 | 5.1 | ▼ |
| CDK4 | 1.1 | 1.9 | |
| TSC1 | 1.1 | 1.1 | |
| FGFR3 | 1 | 1.2 | |
| Rest FDA | 2.1 | | |
| Rest Repurpose | 8.3 | | |
| Rest Experimental | 3.6 | | |
| Rest Other | 5.1 | | |

Actionable: 11% None / 18% None / 32% 3+ / 26% 3+ / 56% 1-2 / 1-2 56%
Best treatment option: 11% None / 18% None / 10% Oth / 14% Oth / 13% Exp / 5% Exp / 41% Off / 28% Off / 25% FDA / 36% FDA

FDA Approved · Drug Repurposing · Experimental/Other Guidelines · Other

## Germline Predisposition

Top potential germline drivers — 172 Patients

| Gene | Type | Breast (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 6.4 | 3.2 | |
| BRCA2 | TSG | 3.6 | 1.5 | |
| MUTYH | TSG | 1.9 | 1.9 | |
| BRCA1 | TSG | 1.4 | 1.1 | |
| ATM | TSG | 1.1 | 1 | |
| MITF | ONC | 0.8 | 0.7 | |
| MSH2 | TSG | 0.6 | 1 | |
| RAD50 | TSG | 0.6 | 0.5 | |
| SDHA | TSG | 0.6 | 0.5 | |

Germline drivers: 80% None / 84% None / 20% 1+ / 16% 1+

STRUCTURAL_VARIANT · SMALL_VARIANT

## WGS vs Panel Coverage

FDA Approved · Drug Repurposing · Other · Experimental/Other Guidelines · None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Experimental/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 253 | 441 | 224 | 41 | 89 |
| Comprehensive 521 gene panel | 244 | 361 | 253 | 48 | 142 |
| Targeted 50 gene panel | 98 | 382 | 116 | 58 | 394 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.28 | 0.9 | 0.77 | 0.29 | 2.2 |
| Comprehensive 521 gene panel | 0.27 | 0.68 | 0.63 | 0.24 | 1.8 |
| Targeted 50 gene panel | 0.48 | 0.9 | | | 0.9 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: Fusion 5, HMZ Disruption 3, Partial CN Loss 2
Drug Repurposing: HRD 137, Fusion 47, Partial CN Loss 32, HMZ Disruption 14, Partial CN Gain 1
Experimental/Other Guidelines: Partial CN Loss 101, Fusion 21, Partial CN Gain 17, Full CN Gain 7, HMZ Disruption 7
Other: Partial CN Loss 30, HMZ Disruption 12, Full CN Loss 9, Small Variant 6

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 101, Small Variant 68, Splice Site 9, Fusion 5, Full CN Loss 4
Drug Repurposing: Small Variant 199, HRD 137, Fusion 47, Partial CN Loss 32, HMZ Disruption 14
Experimental/Other Guidelines: Full CN Gain 278, Small Variant 152, Partial CN Loss 101, Full CN Loss 28, Fusion 21
Other: Small Variant 102, Partial CN Loss 30, Splice Site 17, HMZ Disruption 12, Full CN Loss 12

Number of Missed Events

# The Genomic And Actionability Landscape Of Colon Carcinoma

## Cohort Metadata

### Data availability
**Number of patients with data**

| | |
|---|---|
| WGS | 175 |
| RNASeq | 31 |
| Age, Sex | 33 |
| Biopsy site | 28 |
| Pretreatment | 2 |
| Treatment | 3 |
| Response | 2 |

### Patients with treatment and response data
**Post-biopsy treatment** / **Responders**

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 0 | 0 |
| Multiple | 1 | 0 |
| Targeted | 1 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 0 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Colon COAD, Pan-Cancer

| | Colon COAD | Pan-Cancer |
|---|---|---|
| TMB High | 25% | 21% |
| MSI High | 8% | 2% |
| WGD | 66% | 56% |
| Diploid Proportion | 30% | 34% |
| GIE HLA LOH | 18% | 19% |
| GIE Overall | 26% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 1% | 6% |

## Mutational Landscape

**Tumor purity** — 56% / 55%
**Clonal mutation fraction** — 95% / 95%
**Tumor mutational burden** — 7.3 (25% High), 4.2 (21% High), TMB per Megabase

### Variant types
Number of variants

| | Colon COAD | Pan-Cancer |
|---|---|---|
| SNV | 18,078 | 10,846 |
| INDEL | 2,421 | 983 |
| Structural | 183 | 150 |
| MNV | 197 | 92 |

**Telomere Length** — 0.76 / 0.82 (Log2 Tumor/Germline length)
**VDJ CDR3 Sequences** — 9 / 6 (Log2 (CDR3 + 1))
**Microsatellite instability** — 0.62 (8%), 0.15 (2%), Instable (MS indels per megabase)

**Mean genome ploidy** — 2.8 / 2.6
**Aneuploidy Score** — 20 / 16
**% Copy number alteration** — 58% / 54%
**% Genome LOH** — 22% / 24%

## Processes Underlying Mutations

- DNA damage repair: 49%
- Ageing: 11%
- Chemical exposure: 6%
- UV light: 3%
- APOBEC: 1%
- Tobacco: 1%
- Unknown: 30%

Colon COAD: 175 Patients
Pan-Cancer: 6790 Patients
Colorectal

Made with bioRender

## Copy Number Alteration Profile

Genes labeled: PUDP, ZNF2, SEMA3, PLPP5, MACROD2, SMAD4, SMAD2, TBMS, ERBB2, MAP2K1, TP53, SMAD3, GPHN, IRS2, RB1, FLT3, CDX2, KRAS, CCND2, FGF1, CCND1, PTEN, CDKN2A, FHIT, CCSER1, APC, CTNNA1, GMDS, PRKN, EGFR, MET, OMF21, WWR1, MBKB, FHIT

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers:** 51% (6+), 44% (6+); 49% (1-5), 54% (1-5)

**Oncogenes:** 15% None / 18% None; 23% 3+ / 32% 3+; 61% 1-2 / 50% 1-2

**TSGs:** 85% 3+ / 61% 3+; 15% 1-2 / 33% 1-2

| Gene | Type | Colon COAD (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| APC | TSG | 77 | 14 | ▲ |
| TP53 | TSG | 76 | 55 | ▲ |
| KRAS | ONC | 37 | 15 | ▲ |
| SMAD4 | TSG | 23 | 8 | ▲ |
| PIK3CA | ONC | 20 | 13 | ▲ |
| BRAF | ONC | 15 | 6.2 | ▲ |
| TCF7L2 | TSG | 14 | 1.9 | ▲ |
| ACVR2A | TSG | 12 | 2 | ▲ |
| PTEN | TSG | 12 | 6 | |
| RNF43 | TSG | 11 | 2.3 | ▲ |
| ERBB2 | ONC | 9.7 | 5.7 | |
| FHIT | TSG | 9.1 | 4.3 | |
| SOX9 | TSG | 8 | 1.9 | ▲ |
| TGFBR2 | TSG | 8 | 2.7 | ▲ |
| ZFP36L2 | TSG | 8 | 2.4 | ▲ |
| CDX2 | ONC | 6.9 | 1 | ▲ |
| FLT3 | ONC | 6.9 | 0.9 | ▲ |
| CCSER1 | TSG | 6.3 | 1.6 | |
| B2M | ONC | 5.7 | 1.9 | |
| FBXW7 | TSG | 5.7 | 2.8 | |
| PIK3R1 | TSG | 5.7 | 1.7 | ▲ |
| PRKN | TSG | 5.7 | 1.9 | |
| AMER1 | TSG | 5.1 | 1.4 | ▲ |
| MAP2K4 | TSG | 5.1 | 3.9 | |
| SMAD3 | TSG | 5.1 | 1.1 | ▲ |
| ARID1A | TSG | 4.6 | 6 | |
| IRS2 | ONC | 4.6 | 0.8 | ▲ |
| HLA-B | TSG | 4 | 0.8 | ▲ |
| NRAS | ONC | 4 | 0.8 | ▲ |

**Top cancer drivers** — 173 Patients

Legend: AMPLIFICATION, DELETION, MUTATION

## Potentially Actionable Events

**Actionable:** 21% None / 18% None; 23% 3+ / 26% 3+; 57% 1-2 / 56% 1-2
**Best treatment option:** 21% None / None; 5% Oth / 14% Oth; Exp / 5% Exp; 42% Off / 28% Off; 31% FDA / 36% FDA

| Gene | Colon COAD (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| KRAS | 35 | 14 | ▲ |
| TMB High | 27 | 21 | ▲ |
| PIK3CA | 19 | 13 | ▲ |
| MSI High | 15 | 3.1 | ▲ |
| BRAF | 13 | 5.9 | ▲ |
| PTEN | 12 | 13 | |
| ERBB2 | 9.7 | 5.6 | |
| NRAS | 3.4 | 2.6 | |
| CHEK2 | 2.9 | 3 | |
| CTNNB1 | 2.9 | 2.7 | |
| MAP2K1 | 2.9 | 0.8 | ▲ |
| ATM | 2.3 | 3.5 | |
| CDKN2A | 2.3 | 24 | ▼ |
| FGFR1 | 2.3 | 3.8 | |
| EGFR | 1.7 | 5.1 | |
| KMT2D | 1.7 | 2.9 | |
| AKT1 | 1.1 | 1.4 | |
| CCND1 | 1.1 | 5.3 | ▼ |
| ERBB3 | 1.1 | 0.5 | |
| ERBB4 | 1.1 | 0.5 | |
| MET | 1.1 | 1.7 | |
| BARD1 | 0.6 | 0.1 | ▲ |
| BRCA2 | 0.6 | 2.4 | ▼ |
| Rest FDA | 1.1 | | |
| Rest Repurpose | 4.6 | | |
| Rest Other | 4 | | |

**Top potential actionable events** — 139 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

**Germline drivers:** 88% None / 84% None; 12% 1+ / 16% 1+

| Gene | Type | Colon COAD (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 2.3 | 3.2 | |
| MSH2 | TSG | 1.1 | 1 | |
| MUTYH | TSG | 1.1 | 1.9 | |
| NTHL1 | TSG | 1.1 | 0.4 | |
| PMS2 | TSG | 1.1 | 0.5 | |
| APC | TSG | 0.6 | 0.2 | |
| BARD1 | TSG | 0.6 | 0.1 | ▲ |
| BRCA2 | TSG | 0.6 | 1.5 | |
| BRIP1 | TSG | 0.6 | 0.2 | |

**Top potential germline drivers** — 16 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Exp | None |
|---|---|---|---|---|
| WGS | 55 | 74 | 7 | 36 |
| Comprehensive 521 gene panel | 54 | 75 | | 39 |
| Targeted 50 gene panel | 35 | 76 | | 56 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.55 | 0.89 | 0.22 | 0.33 | 2 |
| Comprehensive 521 gene panel | 0.54 | 0.86 | 0.31 | | 1.9 |
| Targeted 50 gene panel | 0.27 | 0.66 | | | 1.2 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved:** Fusion 2
**Drug Repurposing:** Fusion 2, Partial CN Loss 2, HRD 1
**Experimental/Other Guidelines:** Partial CN Loss 8, Partial CN Gain 1
**Other:** Small Variant 2, Partial CN Loss 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved:** TMB High 47, Fusion 2
**Drug Repurposing:** Small Variant 31, Fusion 2, Partial CN Loss 2, Splice Site 2, HRD 1
**Experimental/Other Guidelines:** Full CN Gain 9, Partial CN Loss 8, Full CN Loss 3, Small Variant 2, Partial CN Gain 2
**Other:** Small Variant 20, Partial CN Loss 2, Splice Site 2, Full CN Loss 1

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Colorectal Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

- WGS: 947
- RNASeq: 461
- Age, Sex: 535
- Biopsy site: 513
- Pretreatment: 448
- Treatment: 393
- Response: 349

### Patients with treatment and response data

**Post-biopsy treatment** | **Responders**

- Chemo: 173 | 15 (9%)
- Multiple: 142 | 58 (41%)
- Targeted: 46 | 12 (26%)
- Hormonal: 1 | 0
- Immuno: 4 | 0
- Radio: 32 | 4 (12%)
- Other: 1 | 0
- None or NA: 0 | 0

## Tumor Characteristics

Colorectum ■ Pan-Cancer

| Metric | Colorectum | Pan-Cancer |
|---|---|---|
| TMB High | 24% | 21% |
| MSI High | 4% | 2% |
| WGD | 69% | 56% |
| Diploid Proportion | 26% | 34% |
| GIE HLA LOH | 20% | 19% |
| GIE Overall | 26% | 26% |
| Viral Insertions | 1% | 3% |
| HRD | 1% | 6% |

## Mutational Landscape

**Tumor purity** — 54% / 55%

**Clonal mutation fraction** — 96% / 95%

**Tumor mutational burden** — 7.1 (24% High) / 4.2 (21%)

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Colorectum | 17,740 | 2,252 | 183 | 195 |
| Pan-Cancer | 10,846 | 983 | 180 / 92 | 92 |

**Telomere Length** — 0.88 / 0.82

**VDJ CDR3 Sequences** — 6 / 6

**Microsatellite instability** — 0.55 (4% Instable) / 0.15 (2%)

**Mean genome ploidy** — 2.9 / 2.6

**Aneuploidy Score** — 22 / 16

**% Copy number alteration** — 63% / 54%

**% Genome LOH** — 25% / 24%

## Processes Underlying Mutations

- DNA damage repair: 38%
- Ageing: 12%
- Chemical exposure: 10%
- UV light: 2%
- APOBEC: 2%
- Tobacco: 1%
- Unknown: 34%

Colorectum — 947 Patients

Pan-Cancer — 6790 Patients

Colorectal

## Copy Number Alteration Profile



## Cancer Driver Landscape

### Top cancer drivers

| Gene | Type | Colorectum (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 81 | 55 | ▲ |
| APC | TSG | 79 | 14 | ▲ |
| KRAS | ONC | 44 | 15 | ▲ |
| SMAD4 | TSG | 25 | 8 | ▲ |
| PIK3CA | ONC | 16 | 13 | |
| BRAF | ONC | 12 | 6.2 | ▲ |
| TCF7L2 | TSG | 10 | 1.9 | ▲ |
| PTEN | TSG | 9.5 | 14 | |
| FBXW7 | TSG | 8.6 | 2.8 | ▲ |
| SOX9 | TSG | 8.4 | 1.8 | ▲ |
| ZFP36L2 | TSG | 7.9 | 2.4 | ▲ |
| RNF43 | TSG | 7.8 | 2.3 | ▲ |
| FHIT | TSG | 7.5 | 4.3 | |
| ACVR2A | TSG | 7.2 | 2 | ▲ |
| PRKN | TSG | 7.2 | 1.9 | ▲ |
| ERBB2 | ONC | 6.5 | 5.7 | |
| AMER1 | TSG | 6.1 | 1.4 | ▲ |
| CDX2 | ONC | 6 | 1.1 | |
| TGFBR2 | TSG | 6 | 2.7 | |
| MAP2K4 | TSG | 5.7 | 3.9 | |
| ARID1A | TSG | 5.6 | 6 | |
| FLT3 | ONC | 5.6 | 1.8 | ▲ |
| MACROD2 | TSG | 5.5 | 1.5 | ▲ |
| SMAD3 | TSG | 5.3 | 1.1 | ▲ |
| NRAS | ONC | 5.1 | 2.8 | |
| CCSER1 | TSG | 4.4 | 1.6 | |
| SMAD2 | TSG | 4.1 | 1.2 | ▲ |
| ATM | TSG | 3.5 | 2.9 | ▲ |
| CDKN2A | TSG | 3.3 | 25 | ▼ |

**Somatic drivers:** 6+ (51%/44%), 1-5 (49%/54%)
**Oncogenes:** None (16%/18%), 3+ (23%/32%), 1-2 (61%/50%)
**TSGs:** None, 3+ (81%/61%), 1-2 (18%/33%)

939 Patients

Legend: ■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### Top potential actionable events

| Gene | Colorectum (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| KRAS | 42 | 14 | ▲ |
| TMB High | 24 | 21 | |
| PIK3CA | 15 | 13 | |
| BRAF | 12 | 5.9 | ▲ |
| PTEN | 9.4 | 13 | |
| MSI High | 7.4 | 3.1 | |
| ERBB2 | 6.4 | 5.6 | |
| NRAS | 4.8 | 2.6 | |
| ATM | 4 | 3.5 | |
| CDKN2A | 3.2 | 24 | ▼ |
| CTNNB1 | 3 | 2.7 | |
| FGFR1 | 2.4 | 3.8 | |
| CHEK2 | 1.8 | 3 | |
| MAP2K1 | 1.8 | 0.8 | |
| MET | 1.5 | 1.7 | |
| VEGFA | 1.2 | 0.7 | |
| ERBB3 | 1.1 | 0.5 | |
| KMT2D | 1.1 | 2.9 | |
| TSC2 | 1.1 | 0.8 | |
| AKT1 | 1 | 1.4 | |
| CCND1 | 1 | 5.3 | ▼ |
| BRCA2 | 0.8 | 1.2 | |
| EGFR | 0.8 | 5.1 | ▼ |
| Rest FDA | 6.4 | | |
| Rest Repurpose | 1.4 | | |
| Rest Experimental | | | |
| Rest Other | 2.6 | | |

**Actionable:** None (18%/18%), 3+ (18%/26%), 1-2 (63%/56%)
**Best treatment option:** None (18%/18%), Oth (4%/14%), Exp (5%), Off (47%/28%), FDA (29%/36%)

774 Patients

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### Top potential germline drivers

| Gene | Type | Colorectum (%) | Pan-Cancer (%) |
|---|---|---|---|
| MUTYH | TSG | 3 | 1.9 |
| CHEK2 | TSG | 2.3 | 3.2 |
| MSH2 | TSG | 1.4 | 1 |
| ATM | TSG | 0.7 | 1 |
| BRCA2 | TSG | 0.7 | 1.5 |
| PMS2 | TSG | 0.7 | 1 |
| NTHL1 | TSG | 0.5 | 0.4 |
| RAD54L | TSG | 0.5 | 0.4 |
| APC | TSG | 0.4 | 0.2 |

**Germline drivers:** None (86%/84%), 1+ (14%/16%)

94 Patients

Legend: ■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines □ Other □ None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA Approved | Drug Repurposing | Exp/Other | None |
|---|---|---|---|---|
| WGS | 274 | 444 | 56 | 157 |
| Comprehensive 521 gene panel | 272 | 436 | 41 | 182 |
| Targeted 50 gene panel | 128 | 489 | 32 | 277 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.41 | 0.92 | 0.26 | 0.24 | 1.8 |
| Comprehensive 521 gene panel | 0.41 | 0.88 | | | 1.7 |
| Targeted 50 gene panel | 0.69 | | | | 1 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Fusion: 5

**Drug Repurposing**
- Partial CN Loss: 18
- Fusion: 17
- HRD: 6
- HMZ Disruption: 1

**Experimental/Other Guidelines**
- Partial CN Loss: 60
- Fusion: 7
- Full CN Gain: 2
- Partial CN Gain: 1
- Splice Site: 1

**Other**
- Partial CN Loss: 22
- HMZ Disruption: 6
- Small Variant: 4
- Full CN Loss: 3
- Splice Site: 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- TMB High: 223
- Fusion: 5
- Small Variant: 2

**Drug Repurposing**
- Small Variant: 159
- Partial CN Loss: 18
- Fusion: 17
- Splice Site: 13
- HRD: 6

**Experimental/Other Guidelines**
- Full CN Gain: 67
- Partial CN Loss: 60
- Small Variant: 15
- Full CN Loss: 14
- Fusion: 7

**Other**
- Small Variant: 72
- Partial CN Loss: 22
- Splice Site: 13
- Full CN Loss: 9
- HMZ Disruption: 6

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.5× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: COREAD

DOIs included: 9256, 50861, 234, 1996, 1993, 219, 80199, 1520, 12192, 305, 169, 5777, 1800, 3030, 218, 2781, 3029, 1519, 1521

Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic domains. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Other events: Fusions, HMZ (Homozygous) Disruptions, Viral inserts, HLA typ(e) assumed not captured by panels.
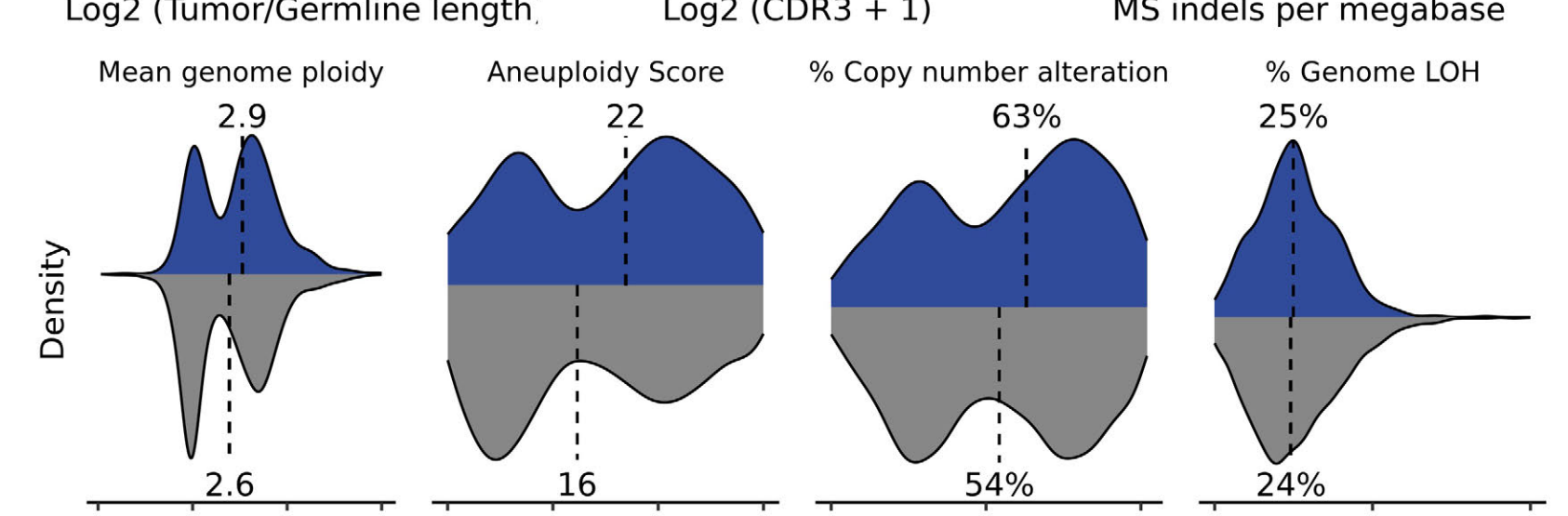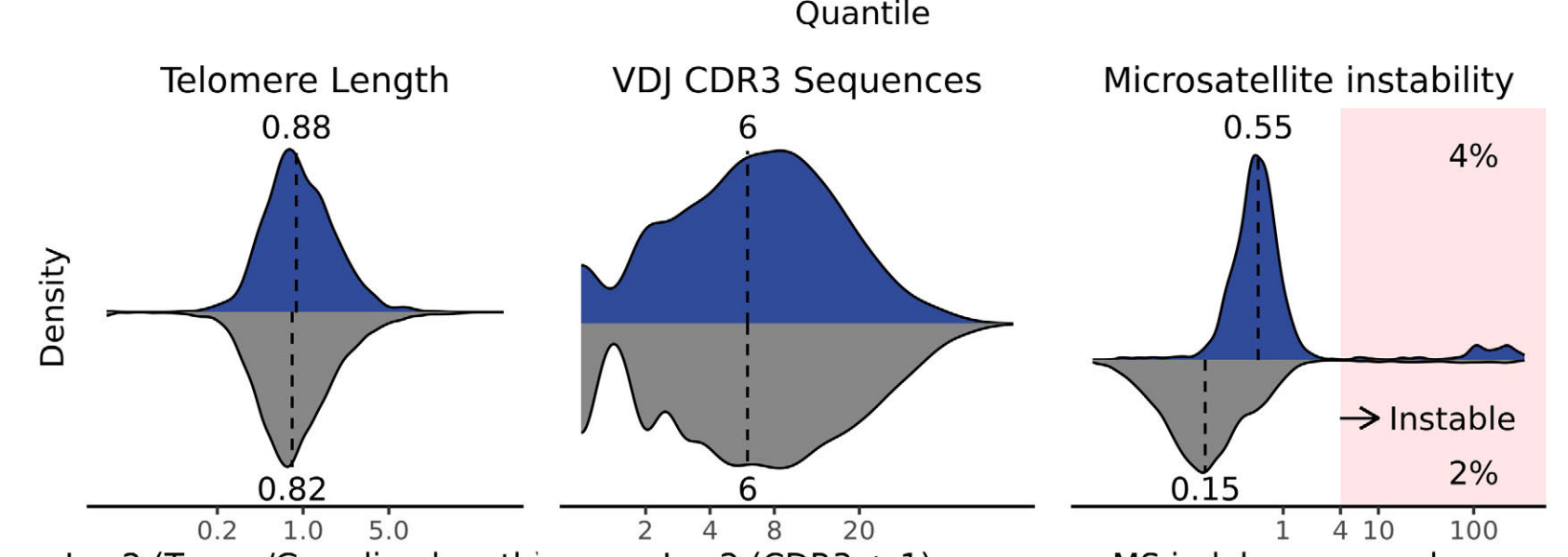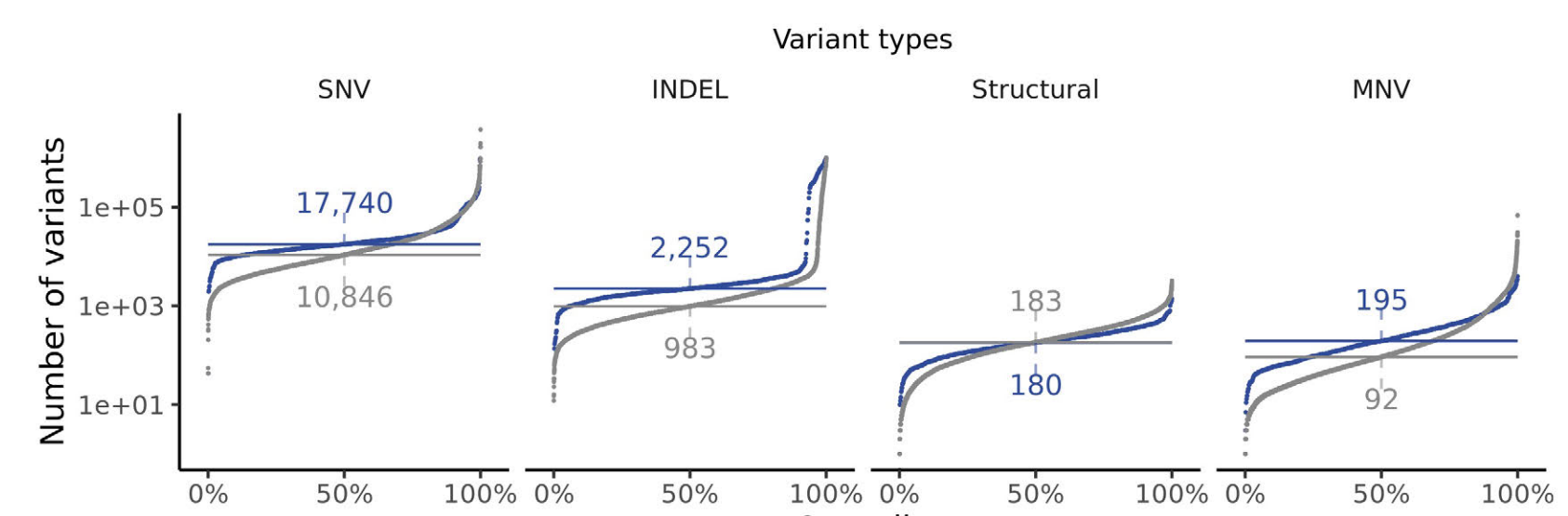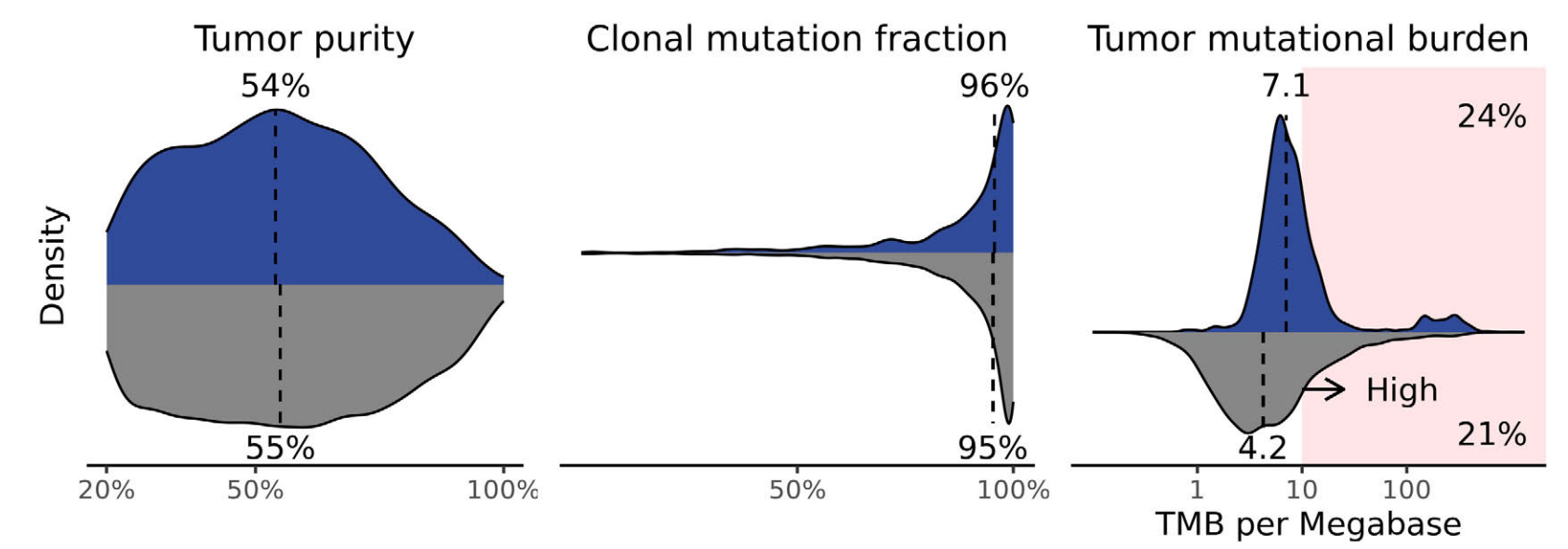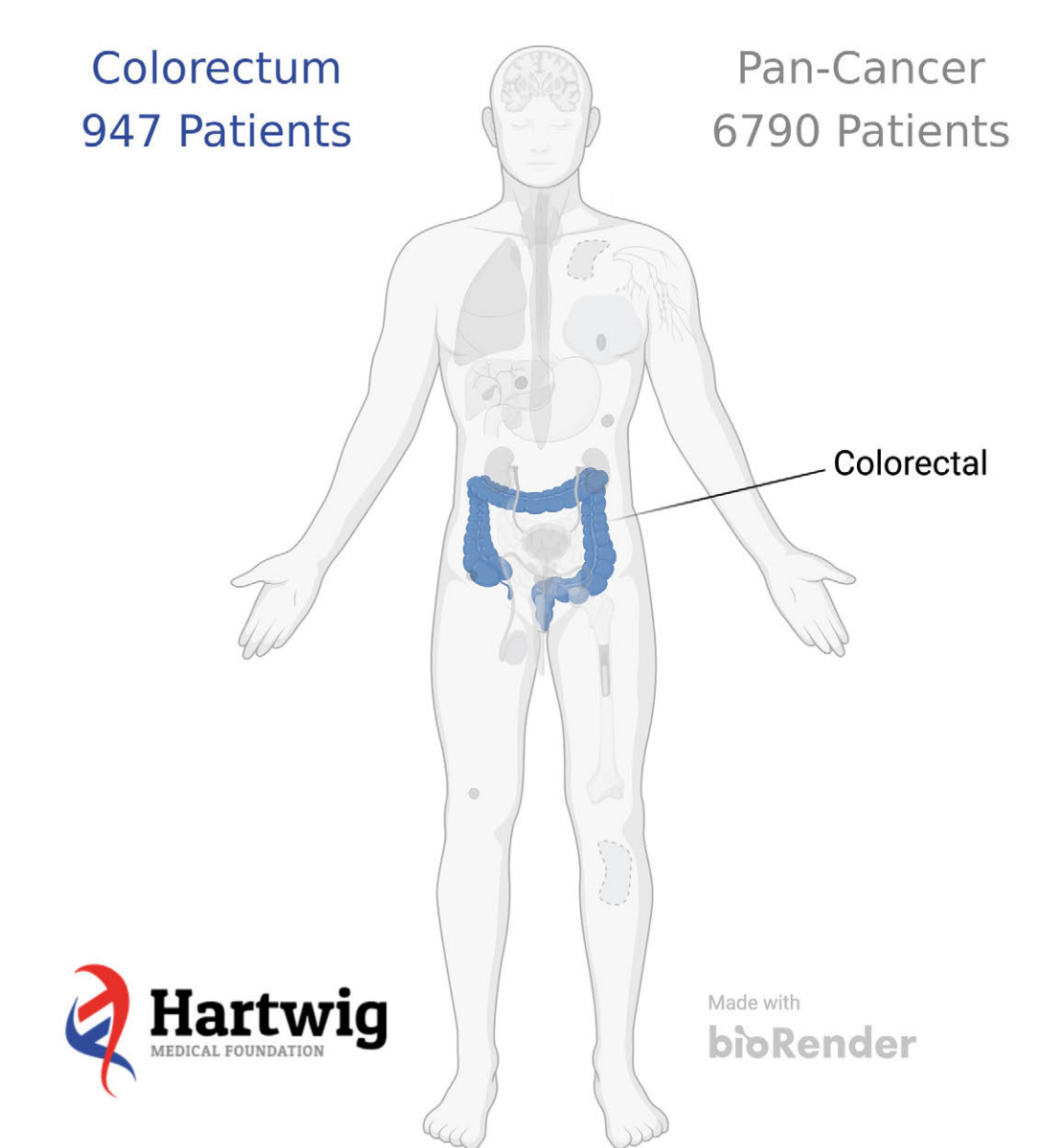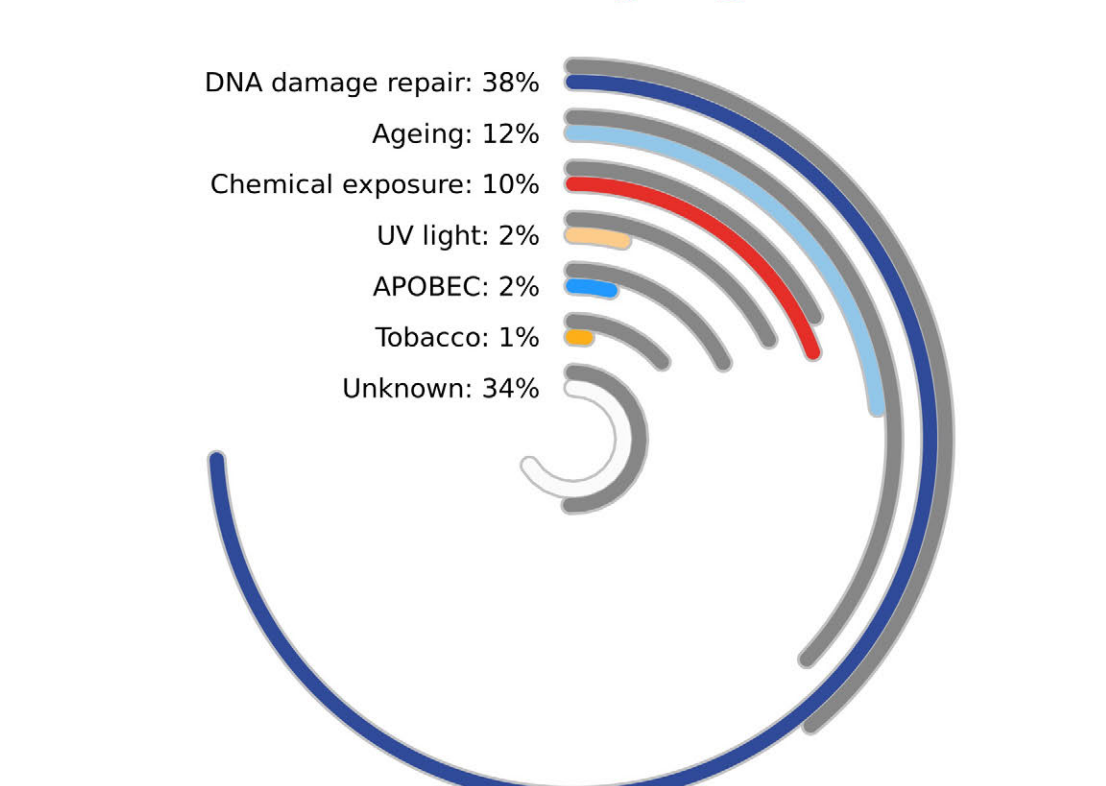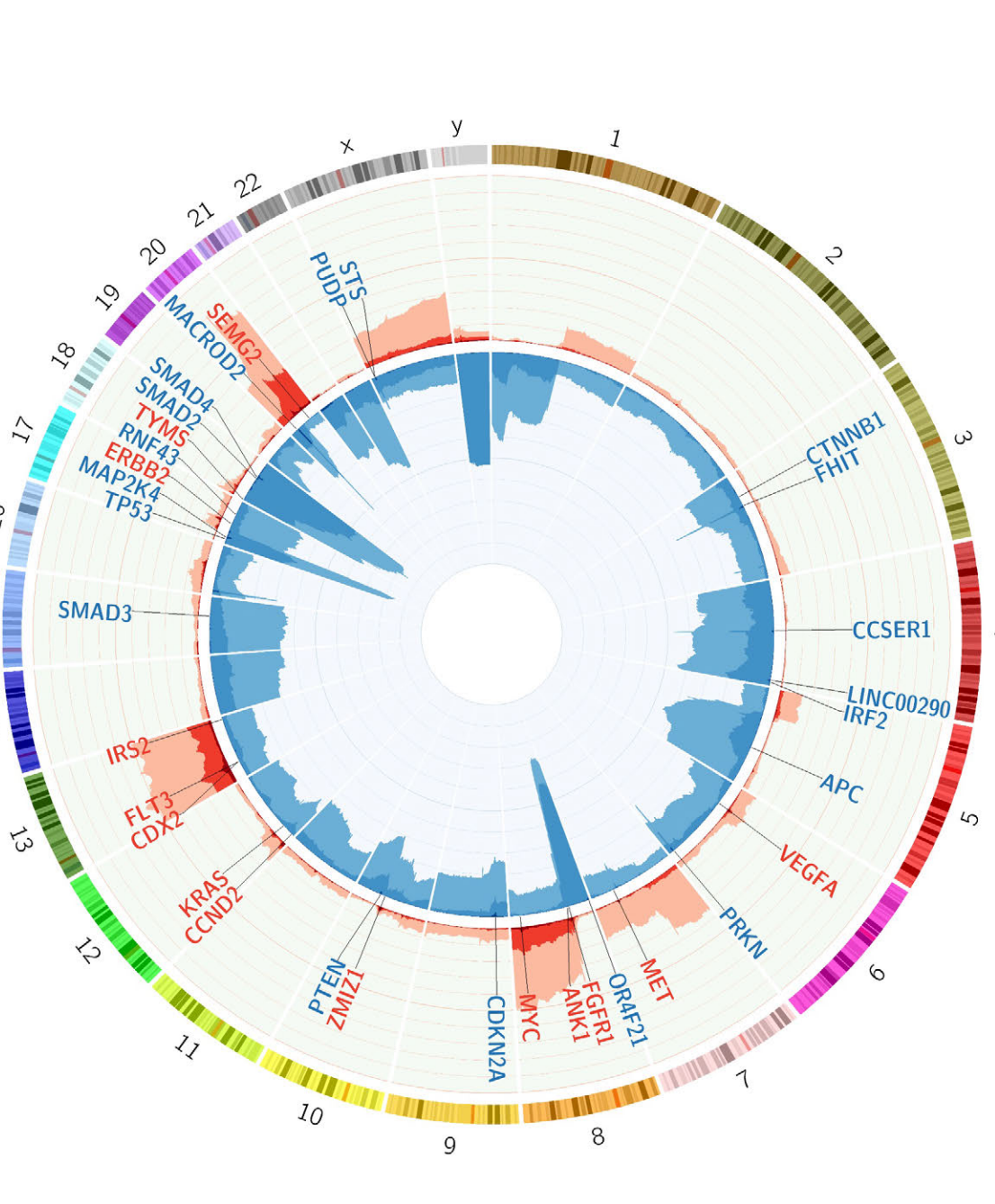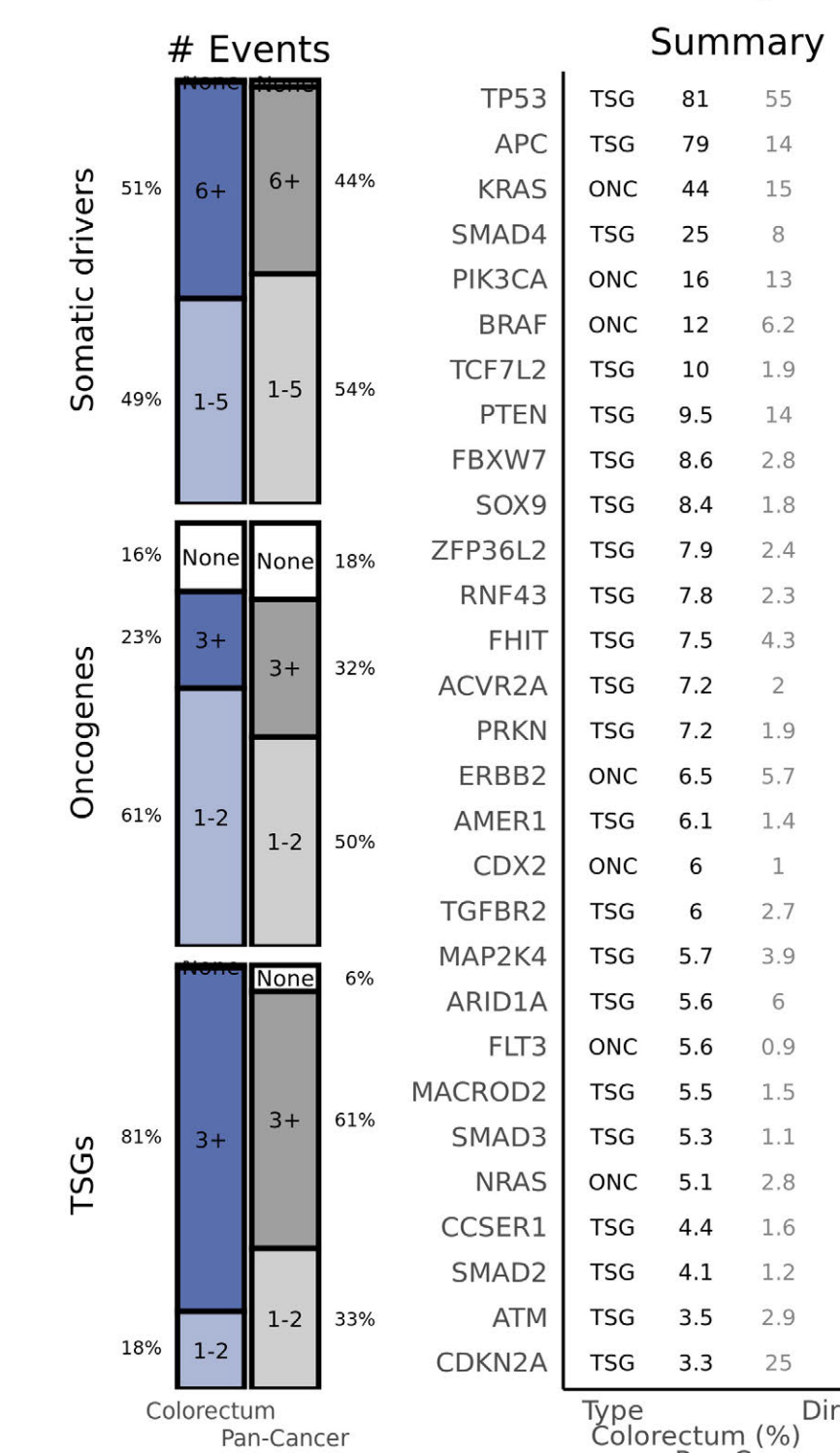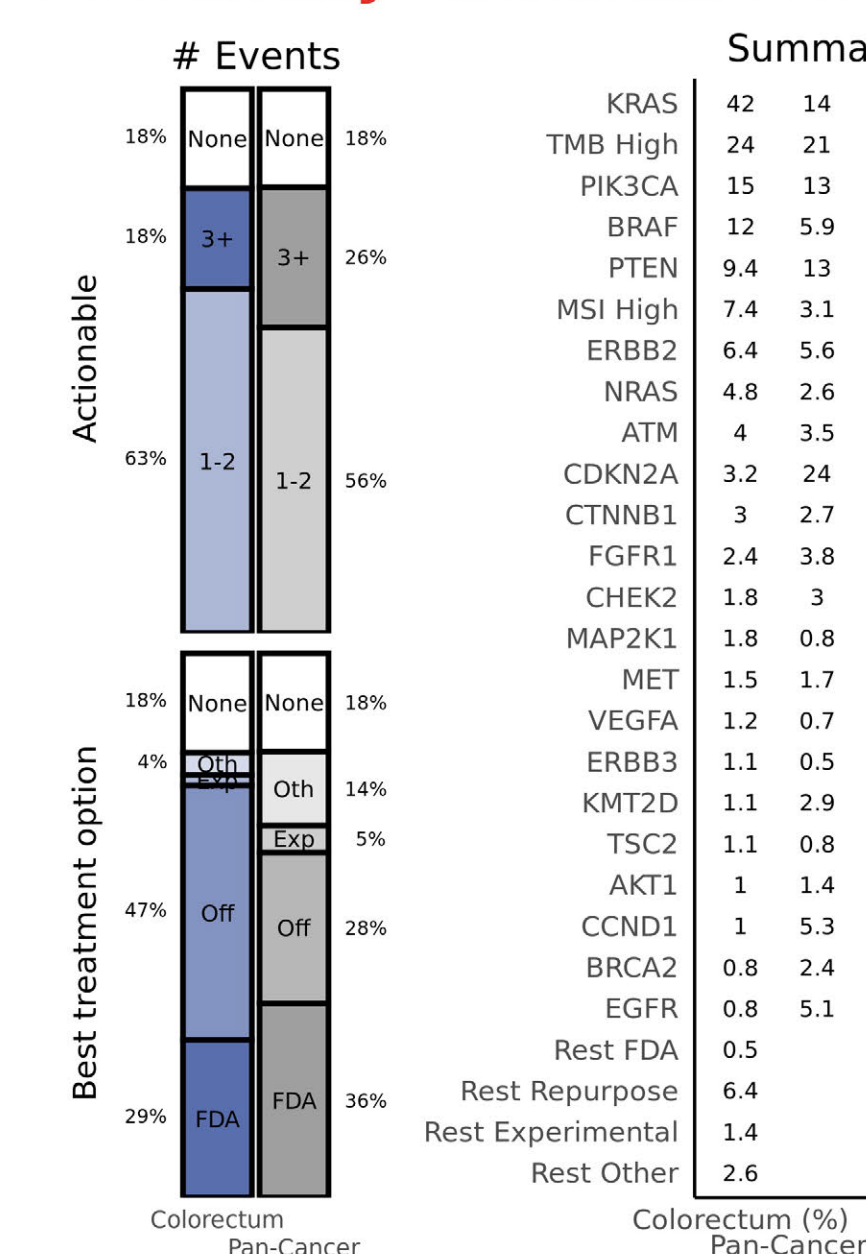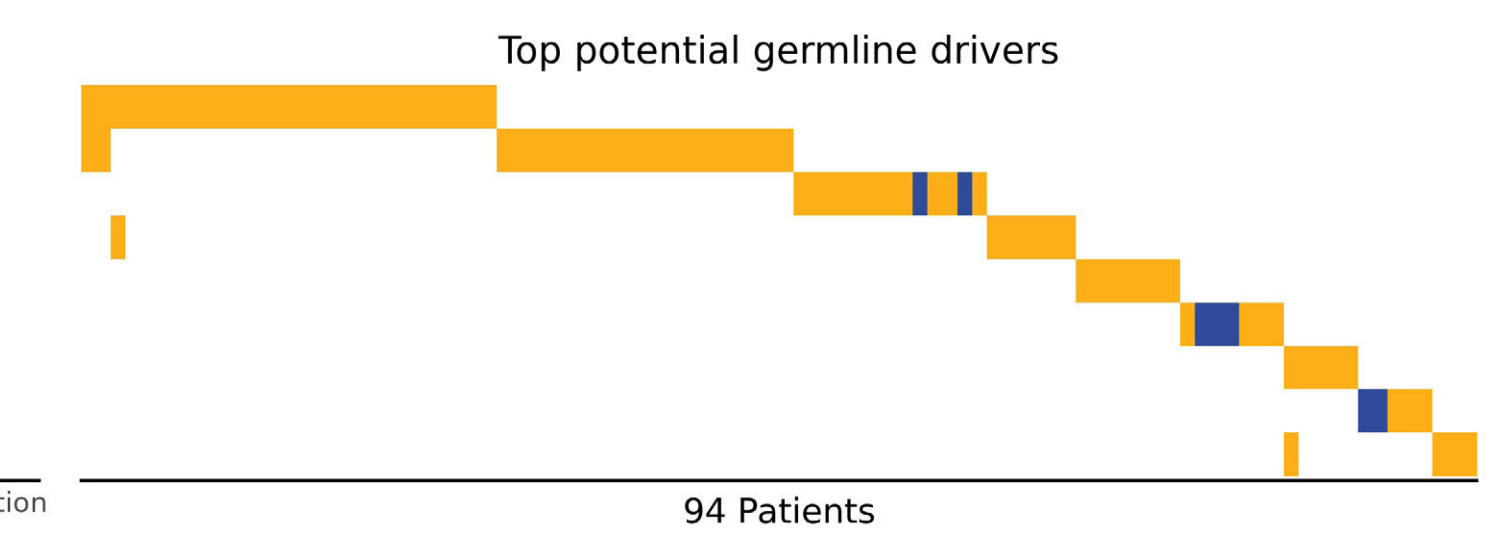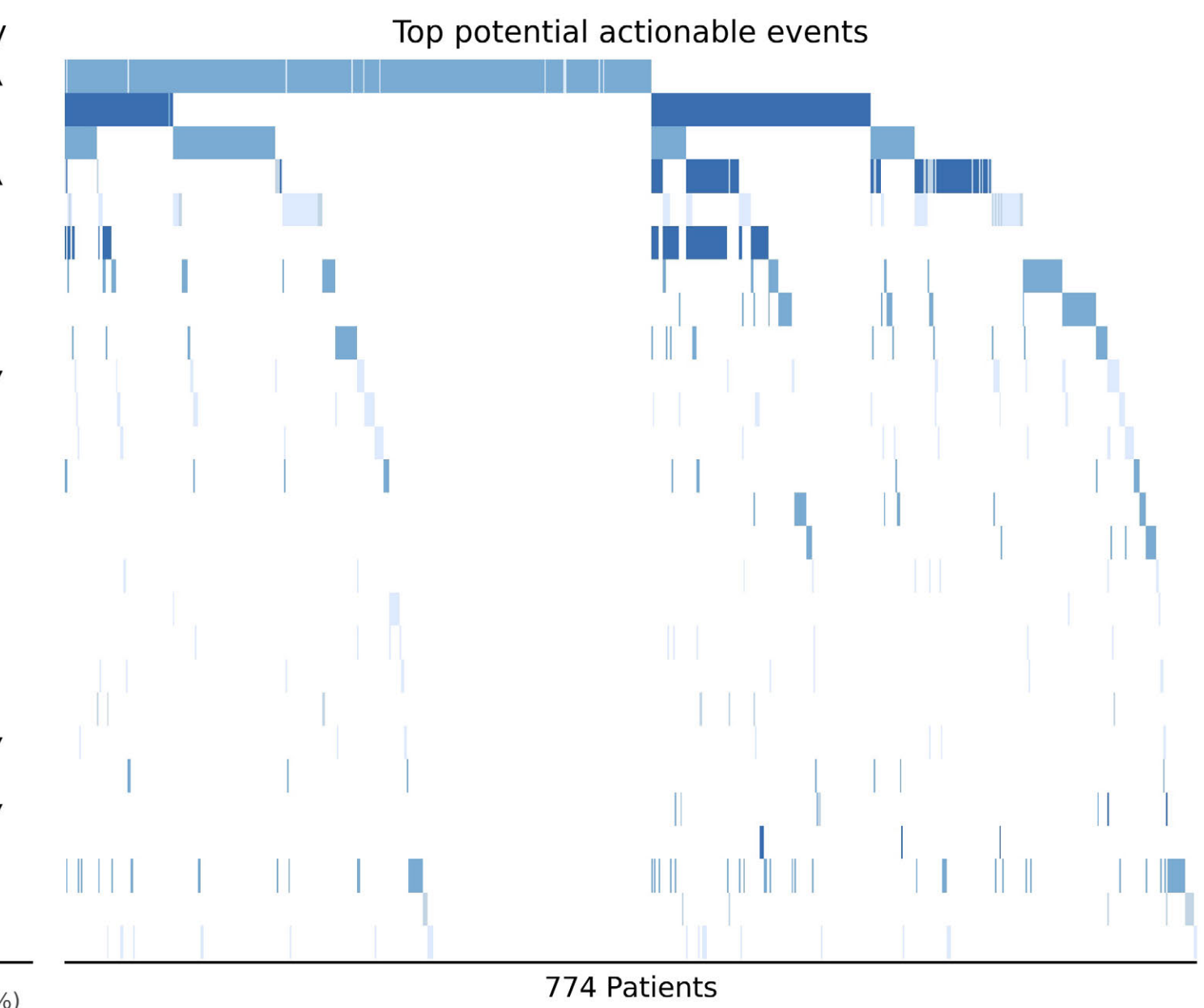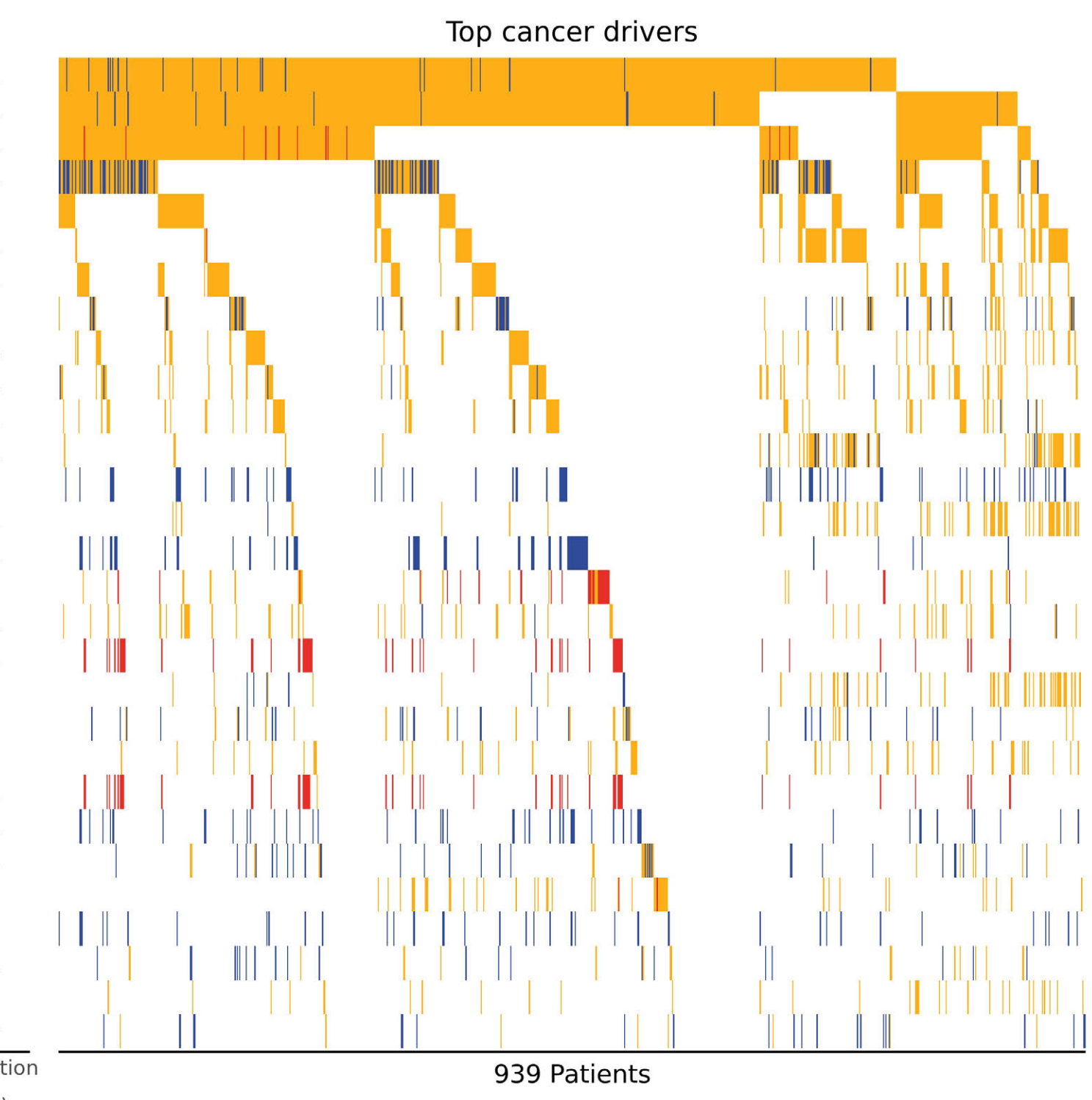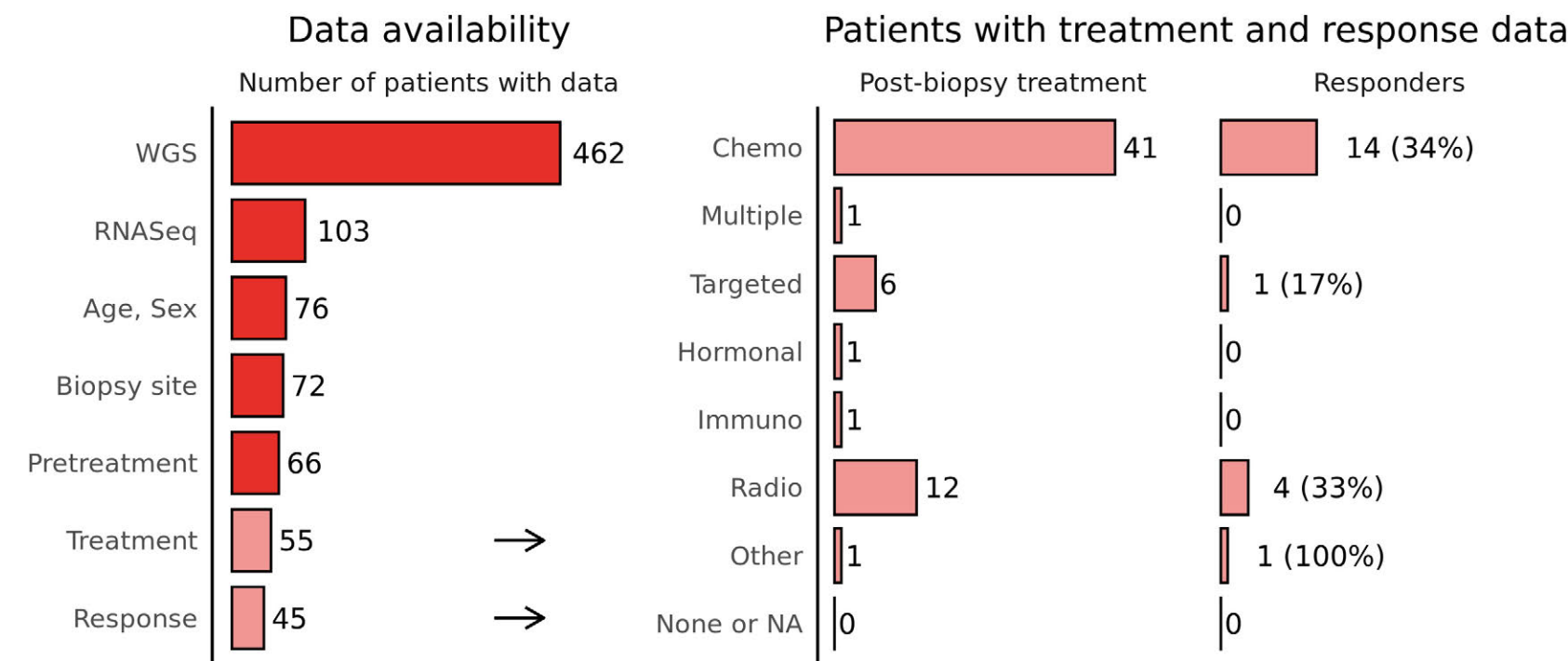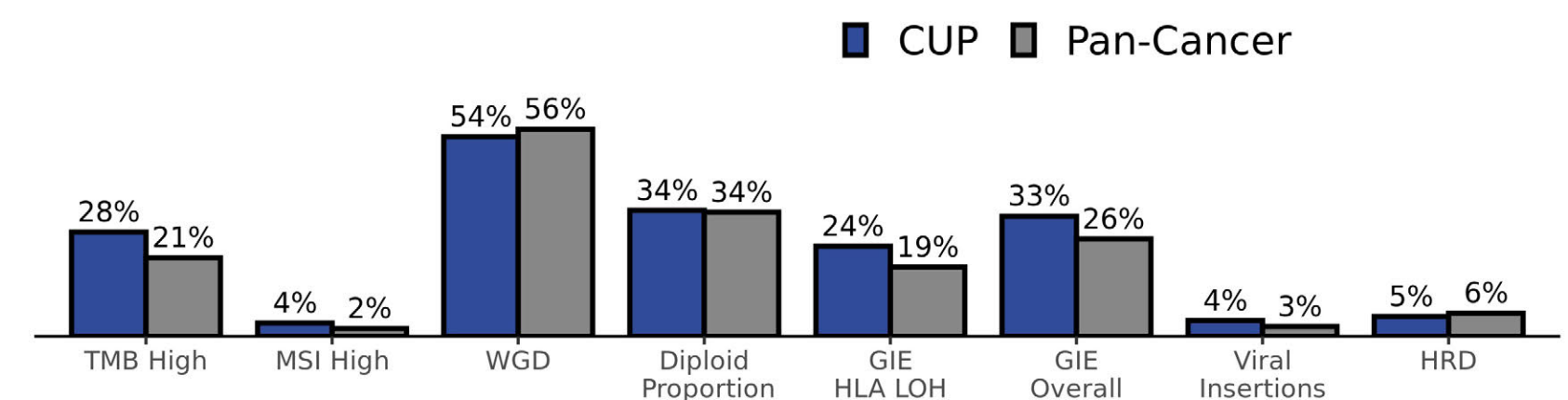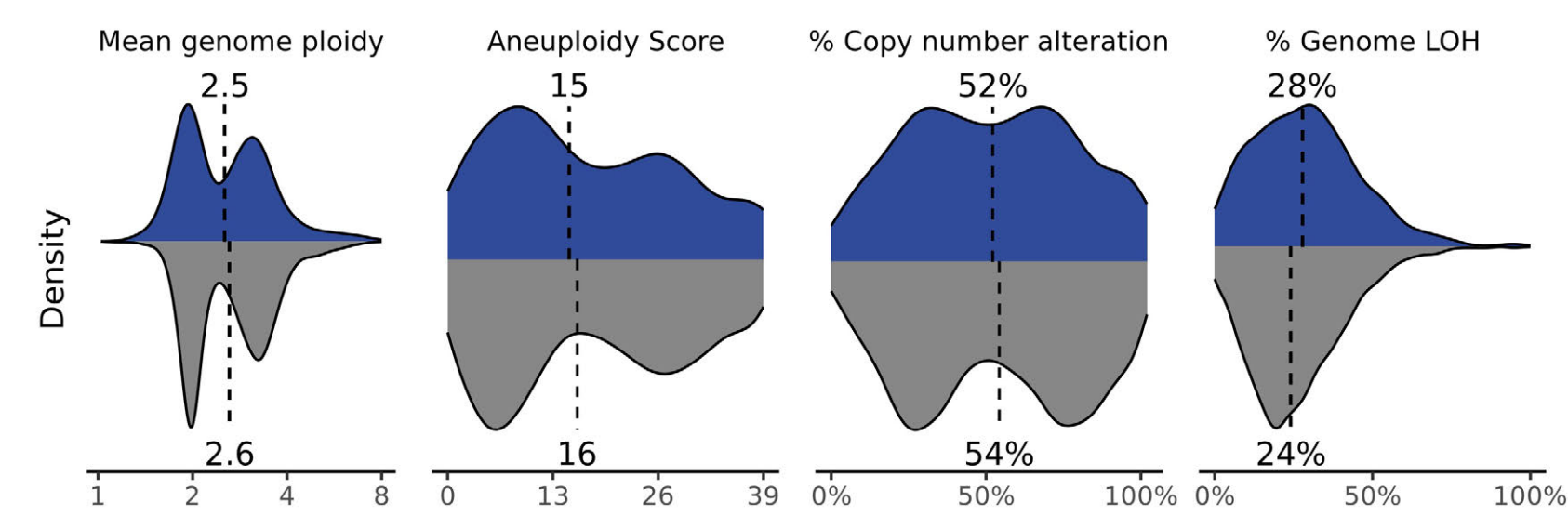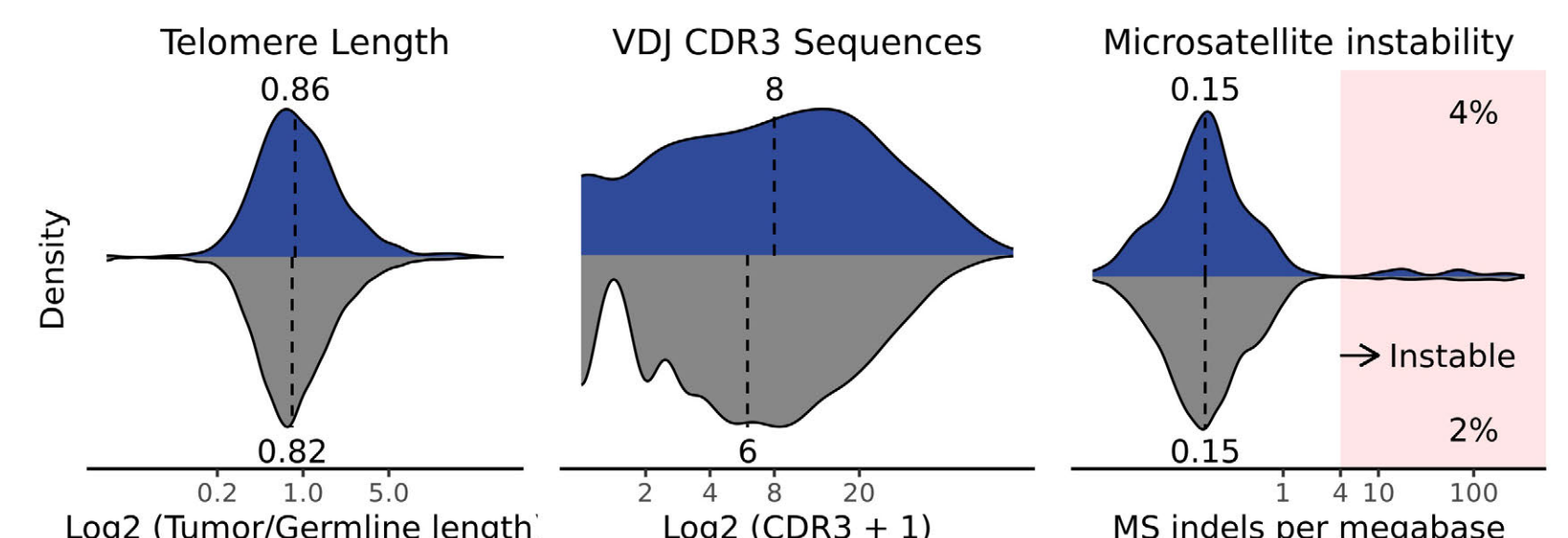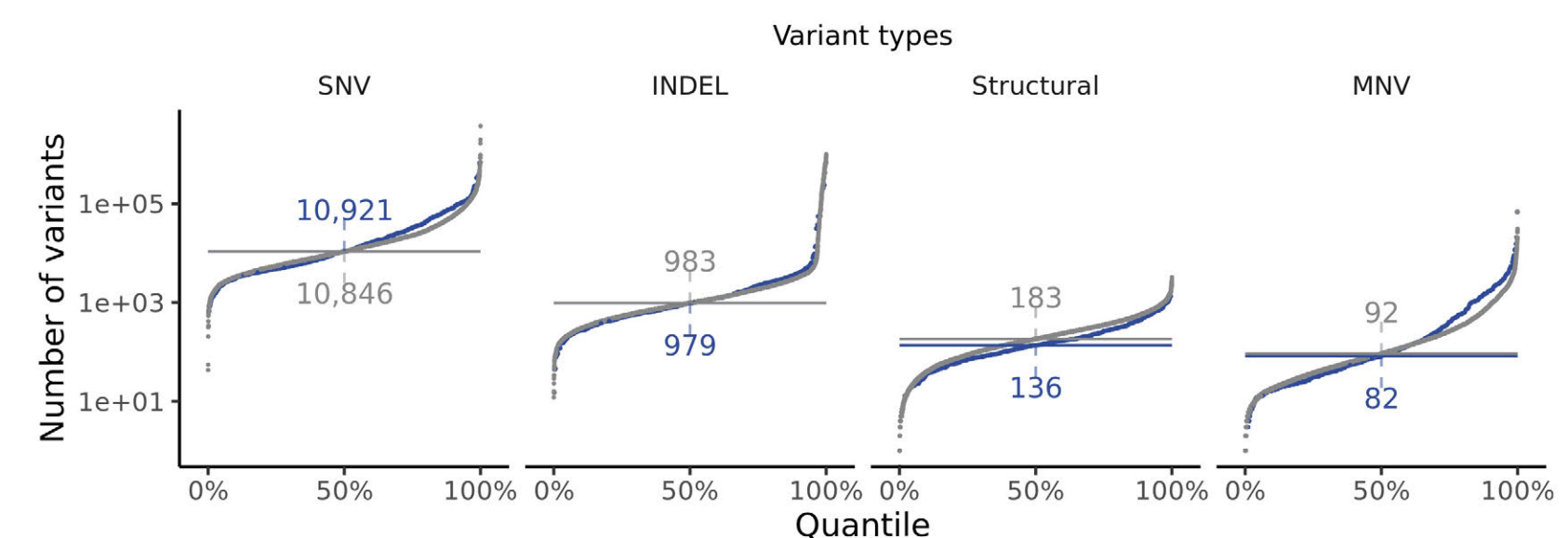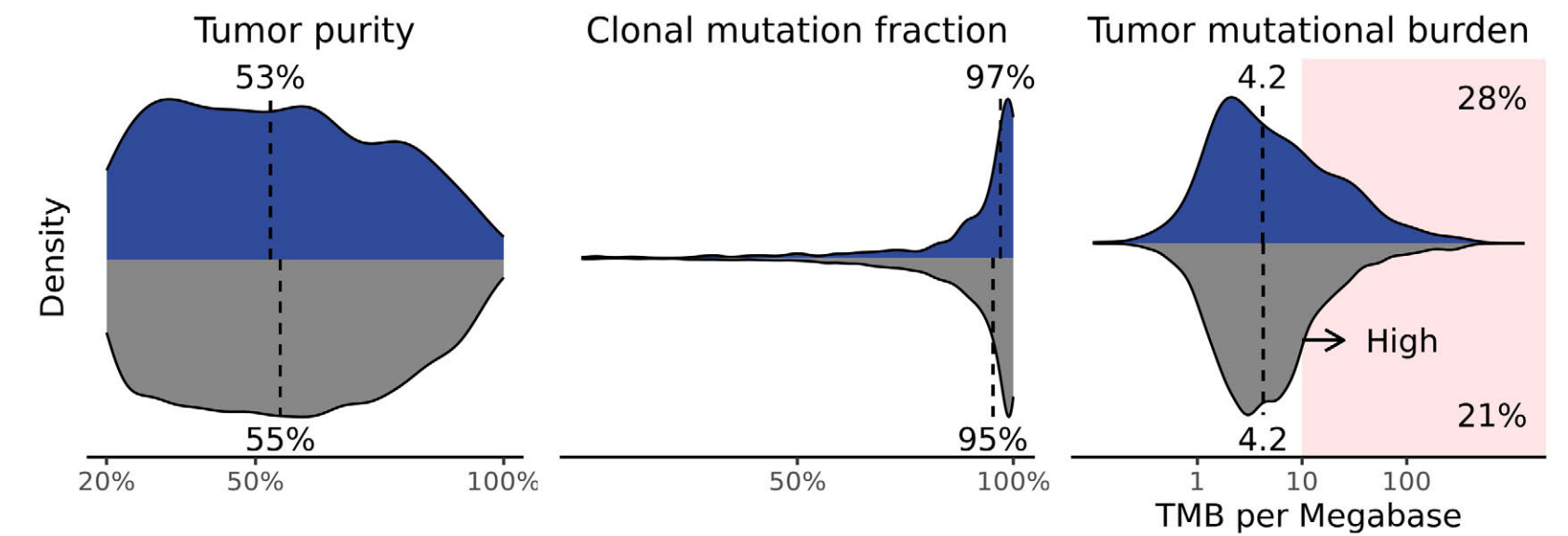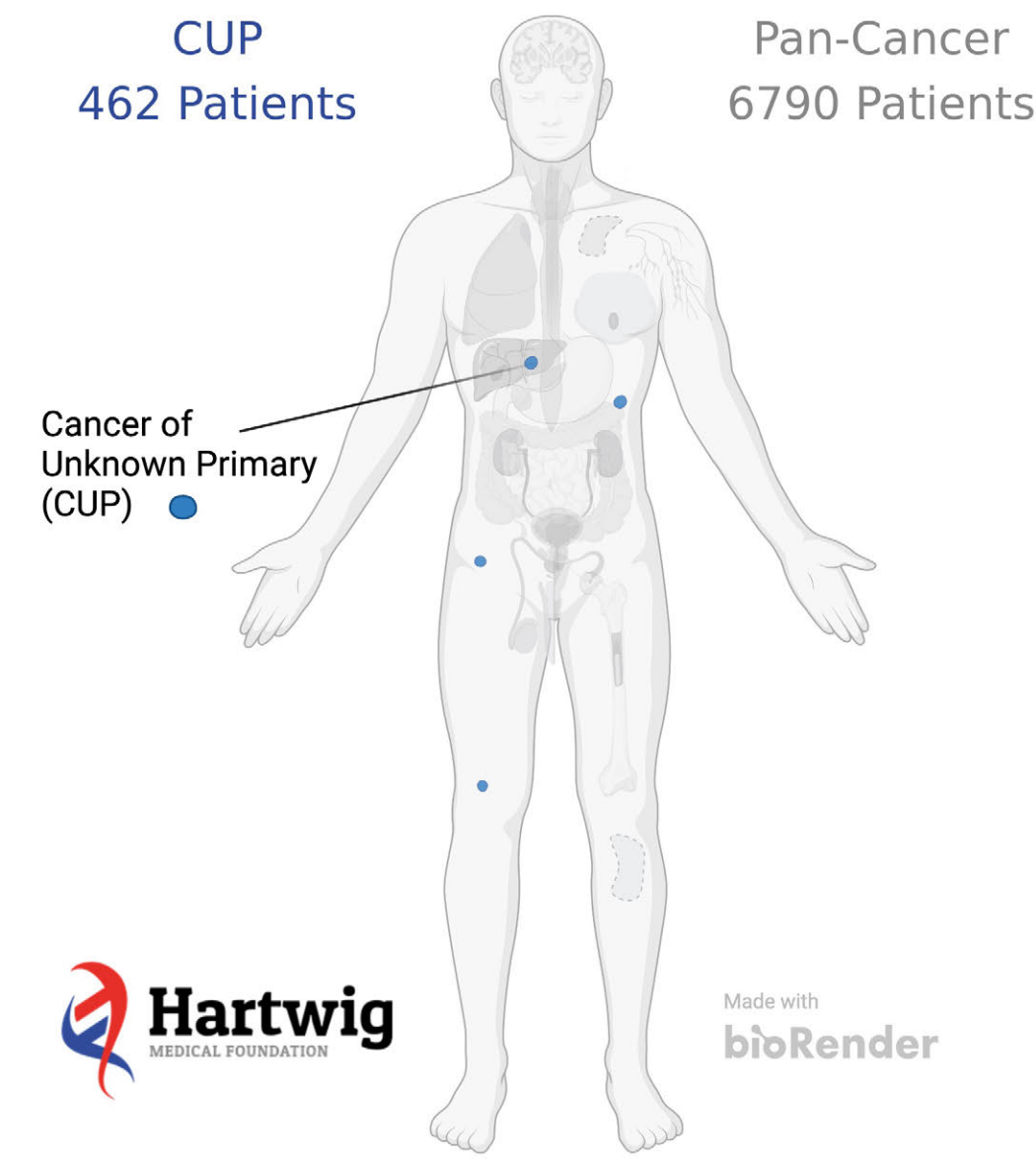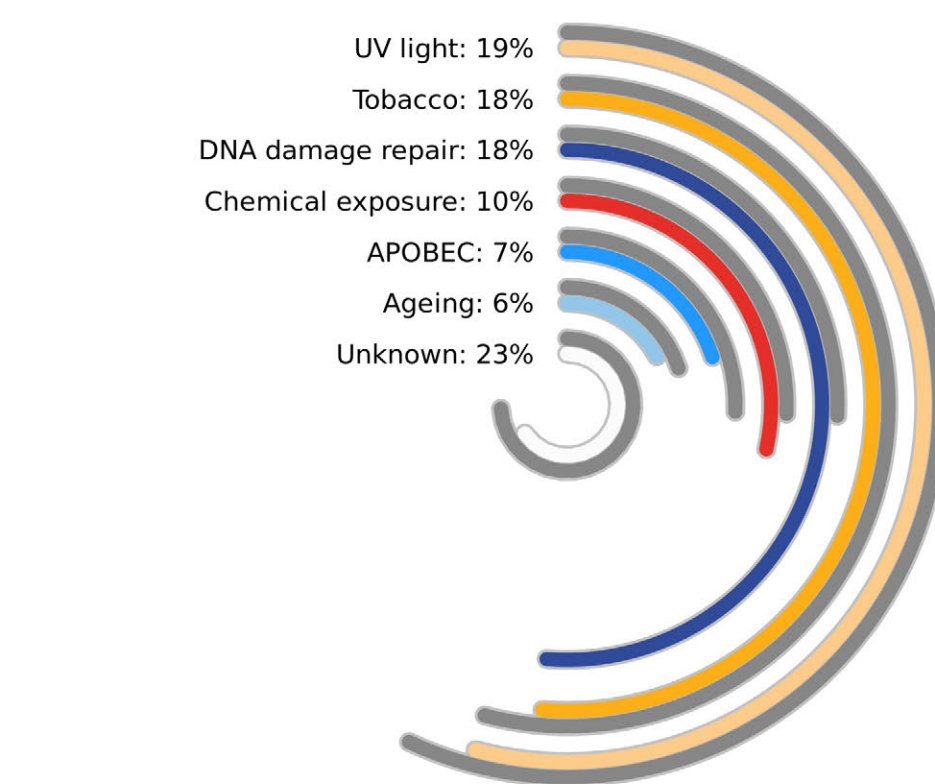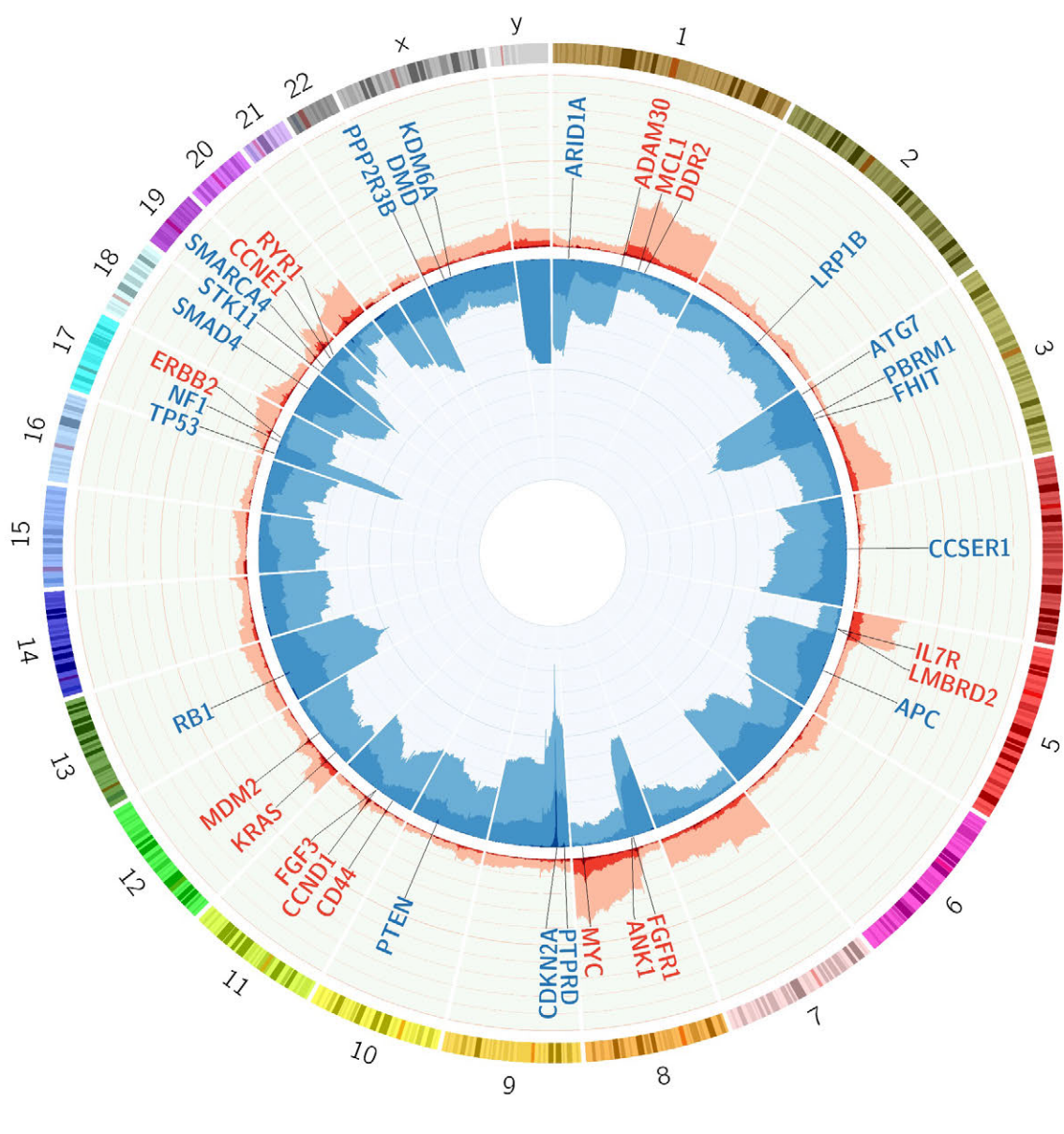** See documentation for further details on the WGS panel coverage study.

# The Genomic And Actionability Landscape Of Cancer Unknown Primary

## Cohort Metadata

### Data availability
**Number of patients with data**

- WGS — 462
- RNASeq — 103
- Age, Sex — 76
- Biopsy site — 72
- Pretreatment — 66
- Treatment — 55 →
- Response — 45 →

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

- Chemo — 41 / 14 (34%)
- Multiple — 1 / 0
- Targeted — 6 / 1 (17%)
- Hormonal — 1 / 0
- Immuno — 1 / 0
- Radio — 12 / 4 (33%)
- Other — 1 / 1 (100%)
- None or NA — 0 / 0

## Tumor Characteristics

■ CUP ■ Pan-Cancer

- TMB High: 28% / 21%
- MSI High: 4% / 2%
- WGD: 54% / 56%
- Diploid Proportion: 34% / 34%
- GIE HLA LOH: 24% / 19%
- GIE Overall: 33% / 26%
- Viral Insertions: 4% / 3%
- HRD: 5% / 6%

## Mutational Landscape

**Tumor purity** — 53% / 55%
**Clonal mutation fraction** — 97% / 95%
**Tumor mutational burden** — 4.2; High 28% / 21%; TMB per Megabase; 4.2

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,921 / 10,846 | 983 / 979 | 183 / 136 | 92 / 82 |

Number of variants vs Quantile

**Telomere Length** — 0.86 / 0.82; Log2 (Tumor/Germline length)
**VDJ CDR3 Sequences** — 8 / 6; Log2 (CDR3 + 1)
**Microsatellite instability** — 0.15 / 0.15; Instable 4% / 2%; MS indels per megabase

**Mean genome ploidy** — 2.5 / 2.6
**Aneuploidy Score** — 15 / 16
**% Copy number alteration** — 52% / 54%
**% Genome LOH** — 28% / 24%

## Processes Underlying Mutations

- UV light: 19%
- Tobacco: 18%
- DNA damage repair: 18%
- Chemical exposure: 10%
- APOBEC: 7%
- Ageing: 6%
- Unknown: 23%

CUP — 462 Patients
Pan-Cancer — 6790 Patients

Cancer of Unknown Primary (CUP)

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## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events
Somatic drivers: 41% 6+ / 44% 6+; 57% 1-5 / 54% 1-5
Oncogenes: 26% None / 18% None; 20% 3+ / 32% 3+; 54% 1-2 / 50% 1-2
TSGs: 4% None / None; 66% 3+ / 61% 3+; 30% 1-2 / 33% 1-2

### Summary (Top cancer drivers — 419 Patients)

| Gene | Type | CUP (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 54 | 55 | |
| CDKN2A | TSG | 32 | 25 | ▲ |
| KRAS | ONC | 18 | 15 | |
| RB1 | TSG | 14 | 11 | |
| PTEN | TSG | 13 | 14 | |
| STK11 | TSG | 11 | 4.1 | ▲ |
| ARID1A | TSG | 9.3 | 6 | |
| TERT | ONC | 9.1 | 13 | |
| KEAP1 | TSG | 8.4 | 2.2 | ▲ |
| SMAD4 | TSG | 7.1 | 8 | ▲ |
| APC | TSG | 6.9 | 14 | ▼ |
| SMARCA4 | TSG | 6.5 | 2.5 | |
| PBRM1 | TSG | 6.1 | 3.2 | |
| PIK3CA | ONC | 5.8 | 13 | ▼ |
| MYC | ONC | 5.2 | 5.7 | |
| NF1 | TSG | 5 | 5 | |
| ARID2 | TSG | 4.8 | 1.8 | |
| KDM6A | TSG | 4.8 | 3.7 | |
| NF2 | TSG | 4.5 | 1.7 | |
| BAP1 | TSG | 4.3 | 2.7 | |
| CCND1 | ONC | 4.3 | 5.6 | |
| BRAF | ONC | 4.1 | 6.2 | |
| FHIT | TSG | 4.1 | 4.3 | |
| PTPRD | TSG | 4.1 | 3 | |
| FGF3 | ONC | 3.9 | 5.2 | |
| IDH1 | ONC | 3.9 | 1.3 | |
| RBM10 | TSG | 3.9 | 1.4 | |
| TGFBR2 | TSG | 3.7 | 2.7 | |
| LRP1B | TSG | 3.5 | 2.1 | |

■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events
Actionable: 27% None / 18% None; 20% 3+ / 26% 3+; 52% 1-2 / 56% 1-2
Best treatment option: 27% None / 18% None; 15% Oth / 14% Oth; 5% Exp; 30% Off / 28% Off; 25% FDA / 36% FDA

### Summary (Top potential actionable events — 335 Patients)

| Event | CUP (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 28 | 24 | |
| TMB High | 24 | 21 | |
| KRAS | 15 | 14 | |
| PTEN | 11 | 13 | |
| HR deficiency | 5 | 5.8 | |
| PIK3CA | 4.8 | 13 | ▼ |
| BRAF | 3.9 | 5.9 | |
| CCND1 | 3.7 | 5.3 | |
| MSI High | 3.7 | 3.1 | |
| ATM | 3.5 | 3.5 | |
| NF2 | 3.2 | 1.6 | |
| IDH1 | 3 | 1 | |
| ERBB2 | 2.8 | 5.6 | |
| NRAS | 2.6 | 2.6 | |
| CTNNB1 | 2.4 | 2.7 | |
| TSC1 | 1.9 | 1.1 | |
| BRCA2 | 1.7 | 2.4 | |
| CHEK2 | 1.7 | 3 | |
| FGFR1 | 1.5 | 3.8 | |
| FGFR2 | 1.5 | 1.1 | |
| FGFR3 | 1.5 | 1.2 | |
| KMT2D | 1.5 | 2.9 | |
| VHL | 1.1 | 1.7 | |
| Rest FDA | 0.6 | | |
| Rest Repurpose | 9.5 | | |
| Rest Experimental | 2.4 | | |
| Rest Other | 5.2 | | |

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events
Germline drivers: 87% None / 84% None; 13% 1+ / 16% 1+

### Summary (Top potential germline drivers — 40 Patients)

| Gene | Type | CUP (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 1.9 | 3.2 | |
| BRCA2 | TSG | 1.7 | 1.5 | |
| ATM | TSG | 1.1 | 1 | |
| TP53 | TSG | 0.9 | 0.5 | |
| BRCA1 | TSG | 0.6 | 1.1 | |
| MSH6 | TSG | 0.6 | 0.4 | |
| NTHL1 | TSG | 0.6 | 0.4 | |
| PMS2 | TSG | 0.6 | 0.4 | |
| RAD51C | TSG | 0.6 | 0.1 | ▲ |

■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other ■ None

### Highest evidence level treatment option identified by test strategy
(# of patients in Hartwig database)

- WGS: 117 / 139 / 40 / 47 / 119
- Comprehensive 521 gene panel: 117 / 118 / 33 / 52 / 142
- Targeted 50 gene panel: 27 / 125 / 25 / 66 / 219

### Average number of identified potentially actionable events identified by test strategy
(Average number of actionable events per patient)

- WGS: 0.31 / 0.56 / 0.26 / 0.62 = 1.7
- Comprehensive 521 gene panel: 0.3 / 0.45 / 0.47 = 1.4
- Targeted 50 gene panel: 0.31 / 0.34 = 0.8

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: Fusion — 3
Drug Repurposing: HRD — 23; Fusion — 14; Partial CN Loss — 14; HMZ Disruption — 1
Experimental/Other Guidelines: Partial CN Loss — 27; Fusion — 2; Full CN Gain — 2; HMZ Disruption — 1; Partial CN Gain — 1
Other: Partial CN Loss — 52; Full CN Loss — 6; HMZ Disruption — 5; Small Variant — 4; Splice Site — 1

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High — 112; Fusion — 3
Drug Repurposing: Small Variant — 57; HRD — 23; Fusion — 14; Partial CN Loss — 14; Splice Site — 10
Experimental/Other Guidelines: Full CN Gain — 45; Partial CN Loss — 27; Small Variant — 7; Fusion — 2; Full CN Loss — 2
Other: Small Variant — 55; Partial CN Loss — 52; Splice Site — 9; Full CN Loss — 6; HMZ Disruption — 5

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).
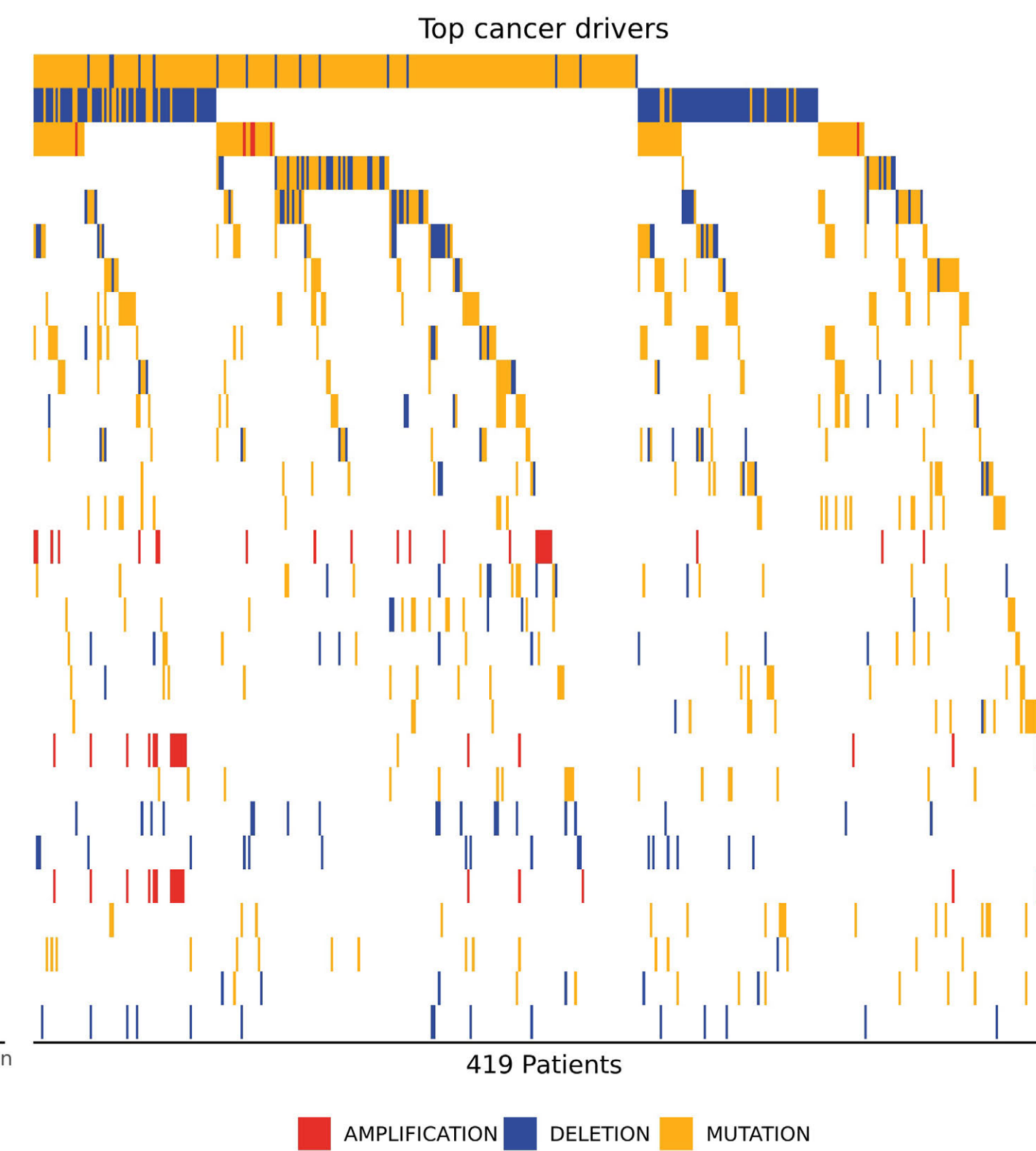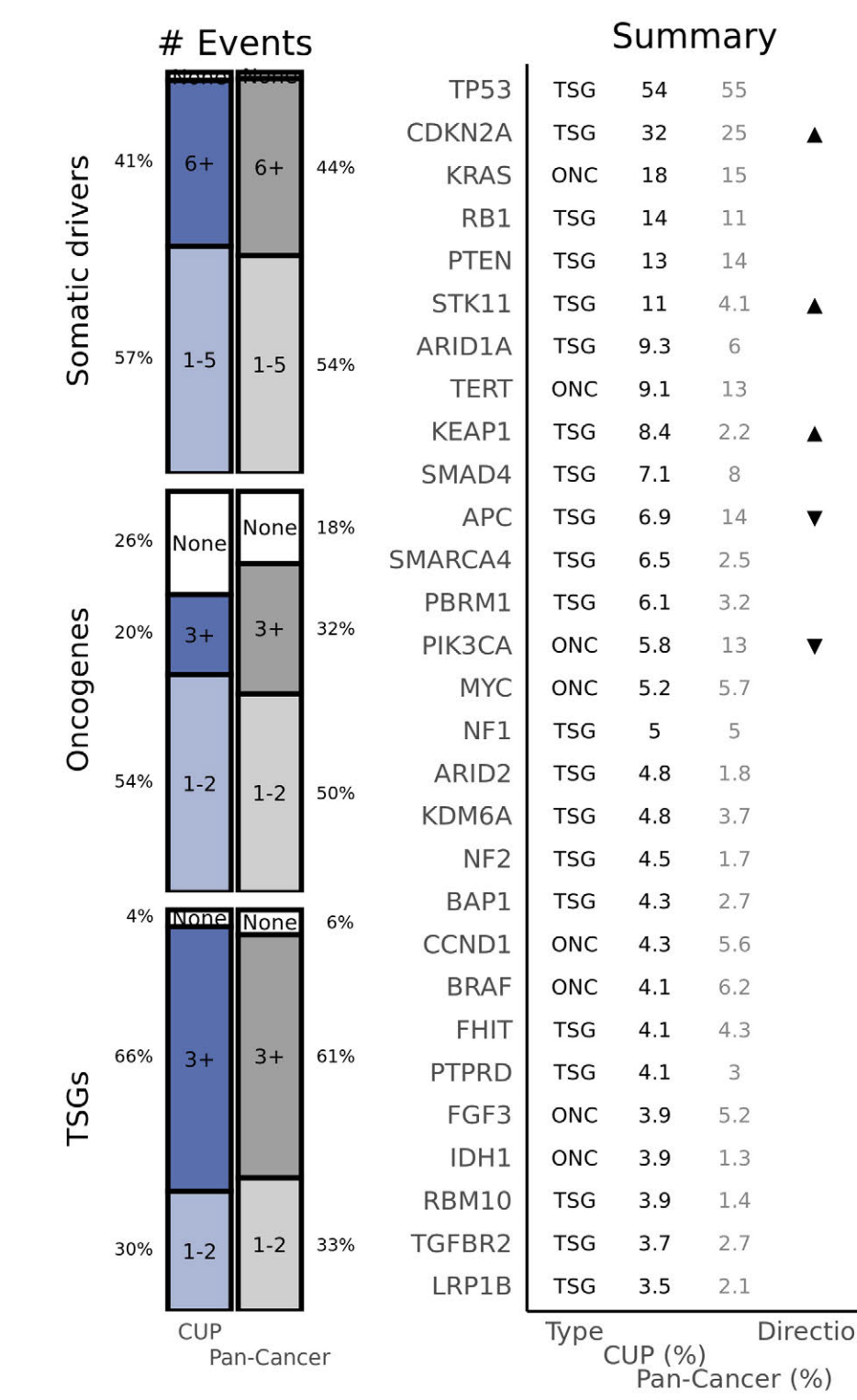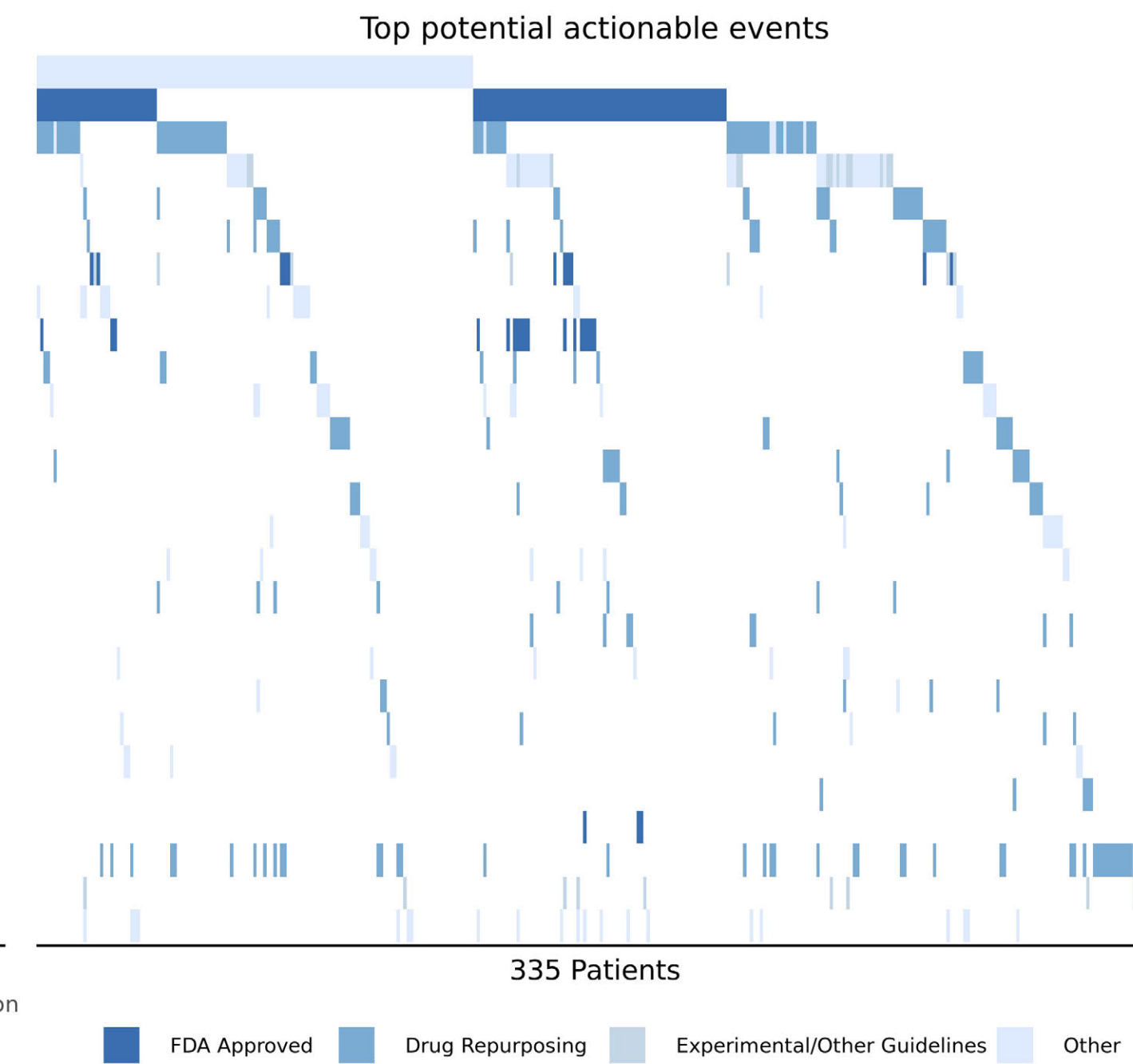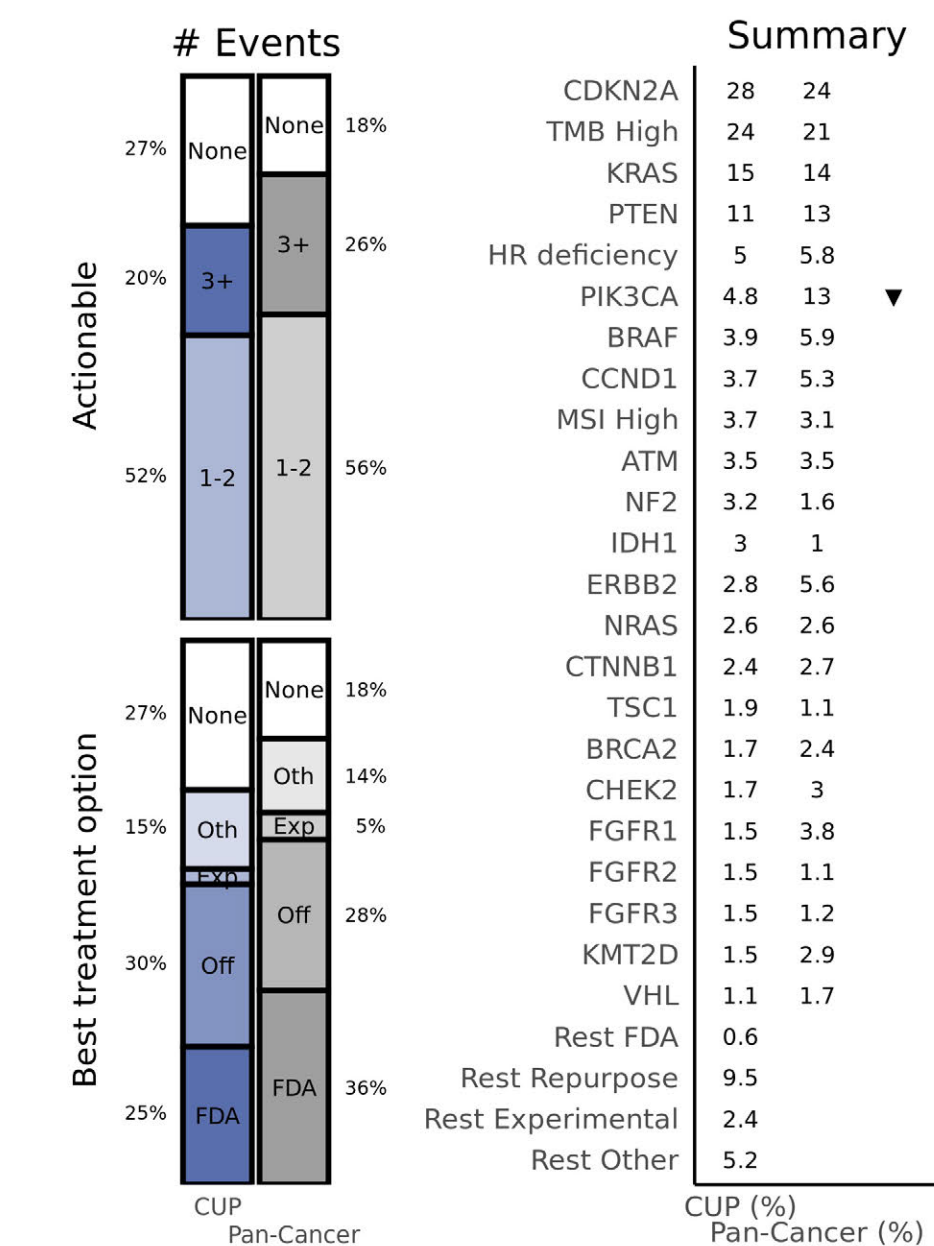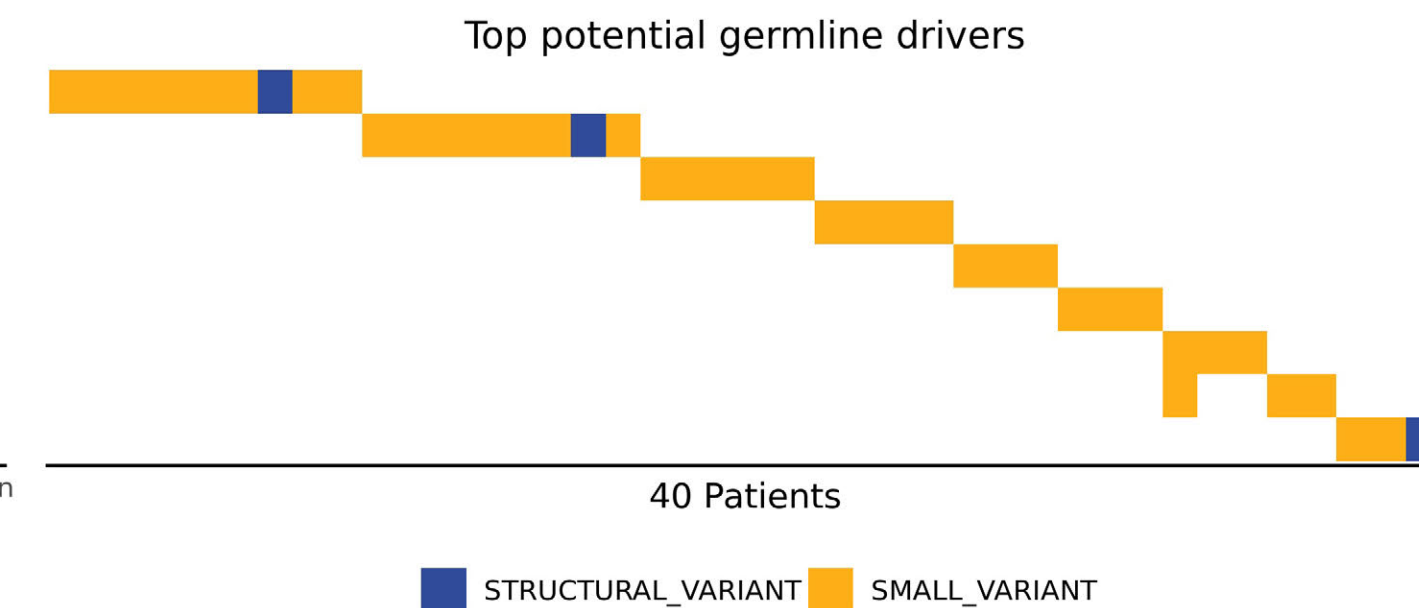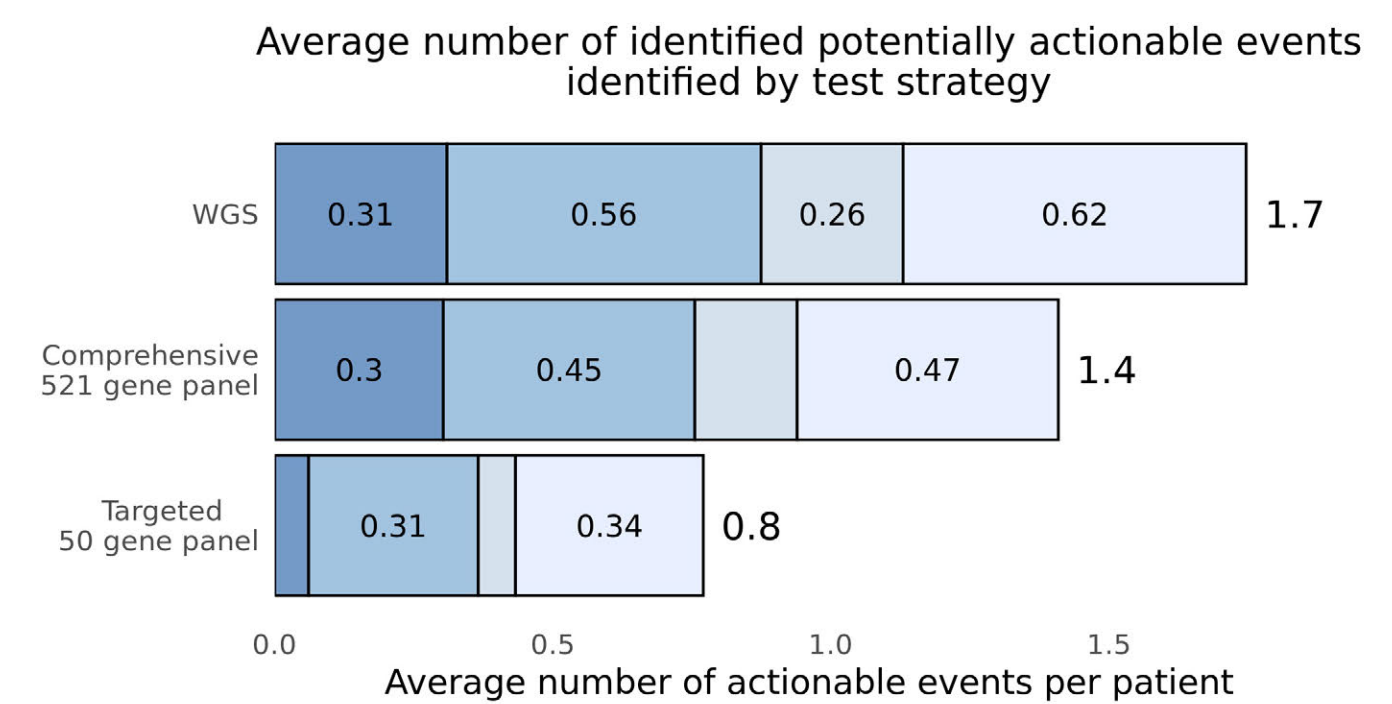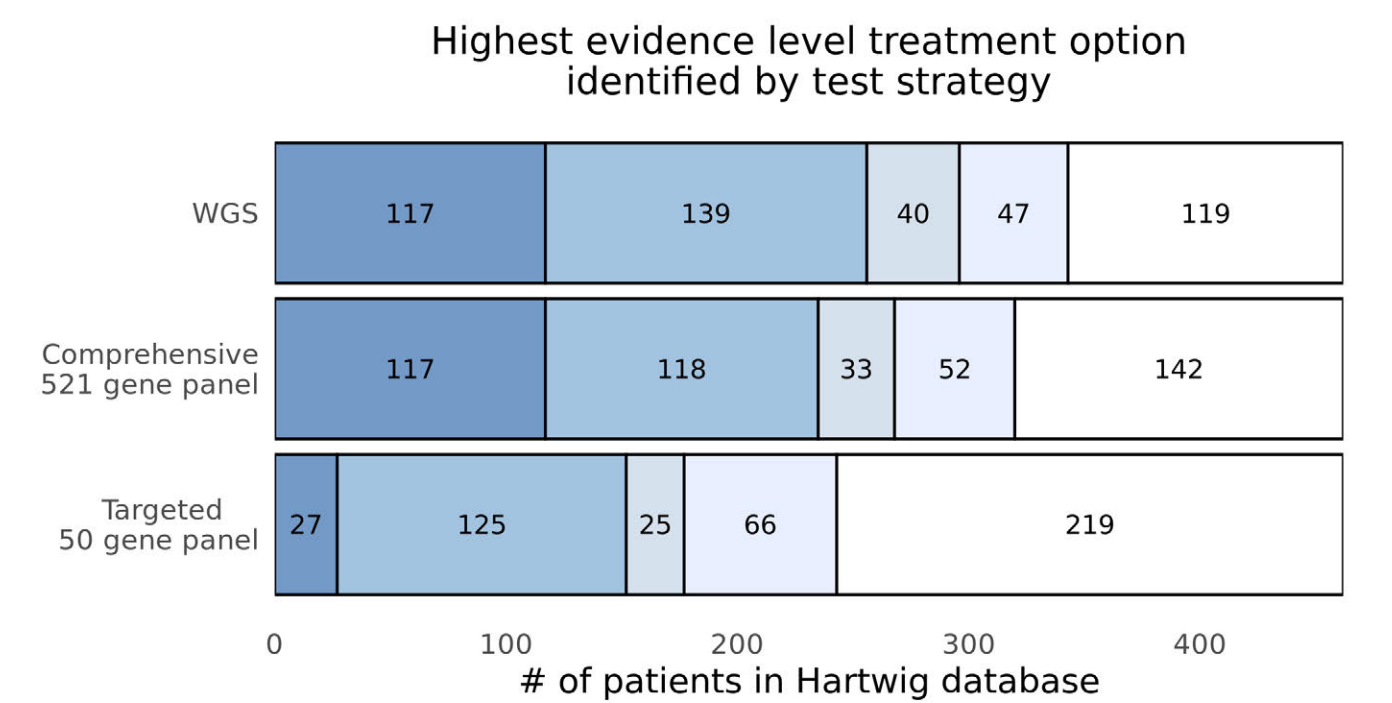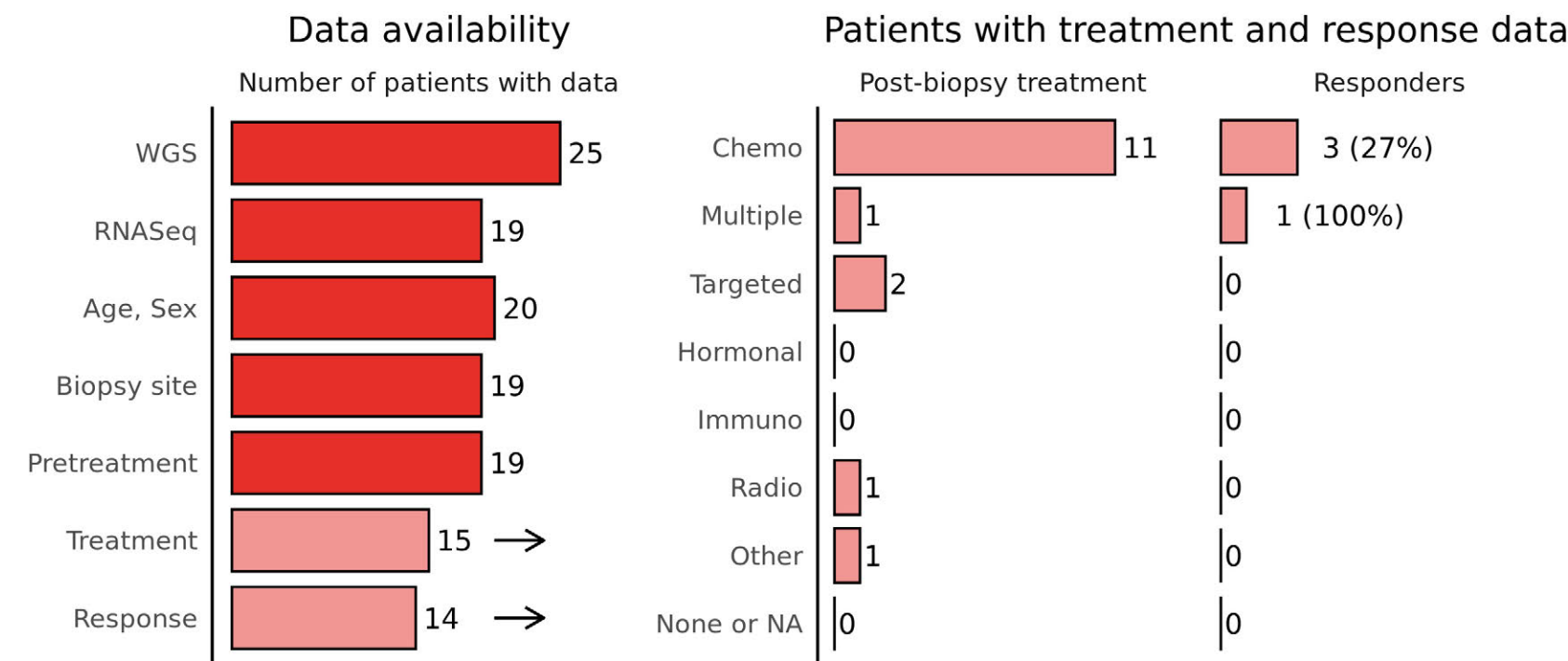
Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: CUP
DOIDs included: 305, 162, 299, 1800, 169, 1749
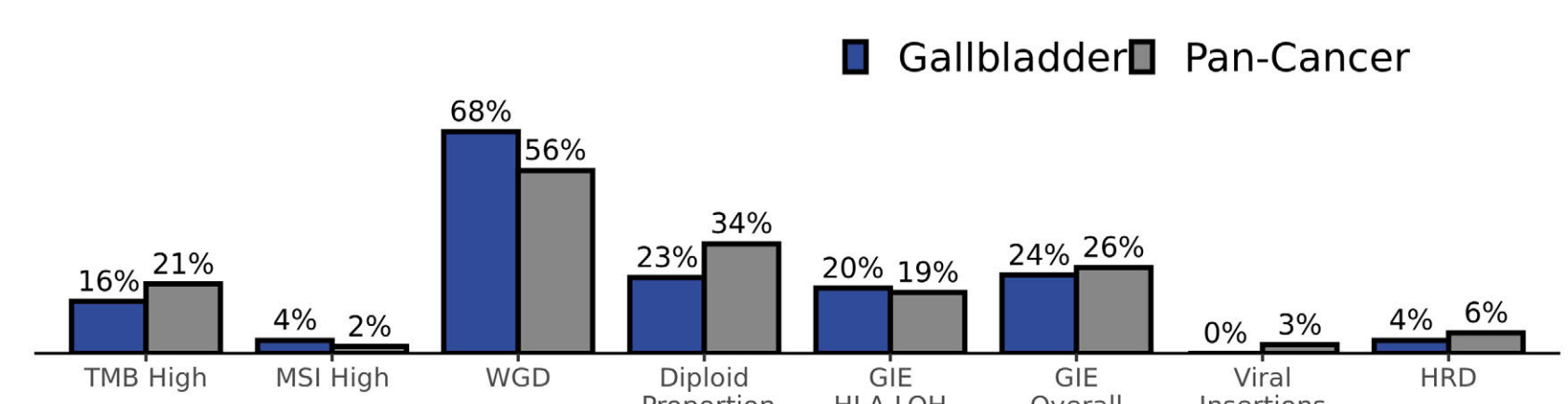Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High captured by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with min copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Distruptions, Viral Insers, HLA type assumed not captured by panels.
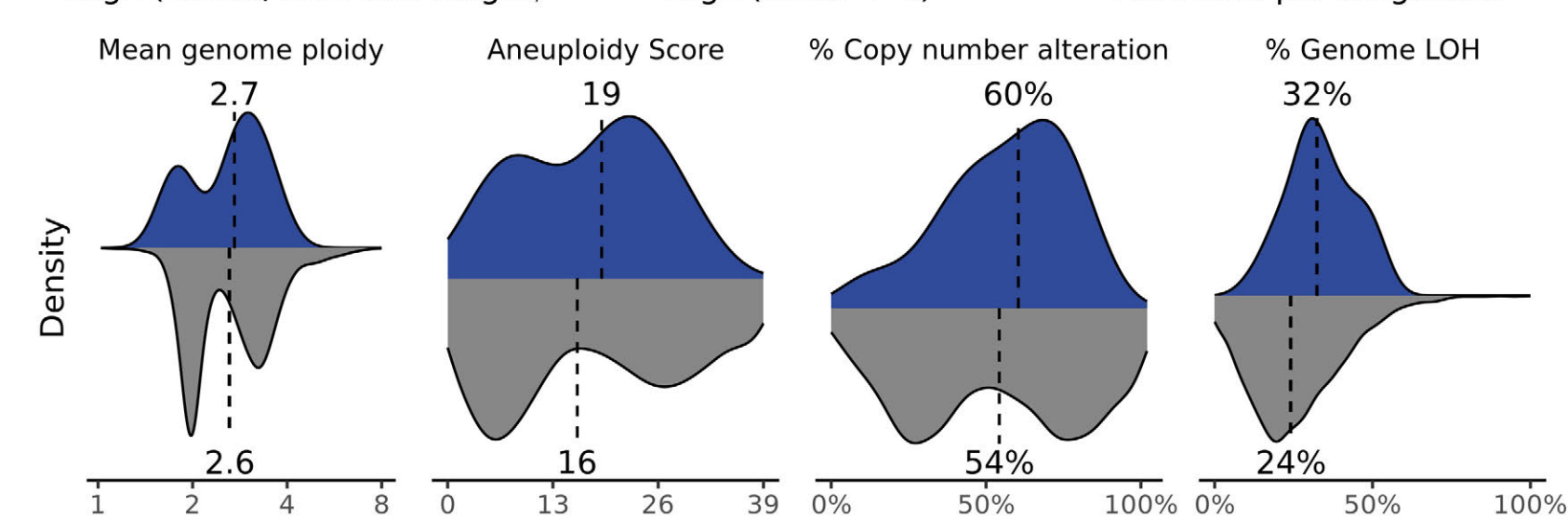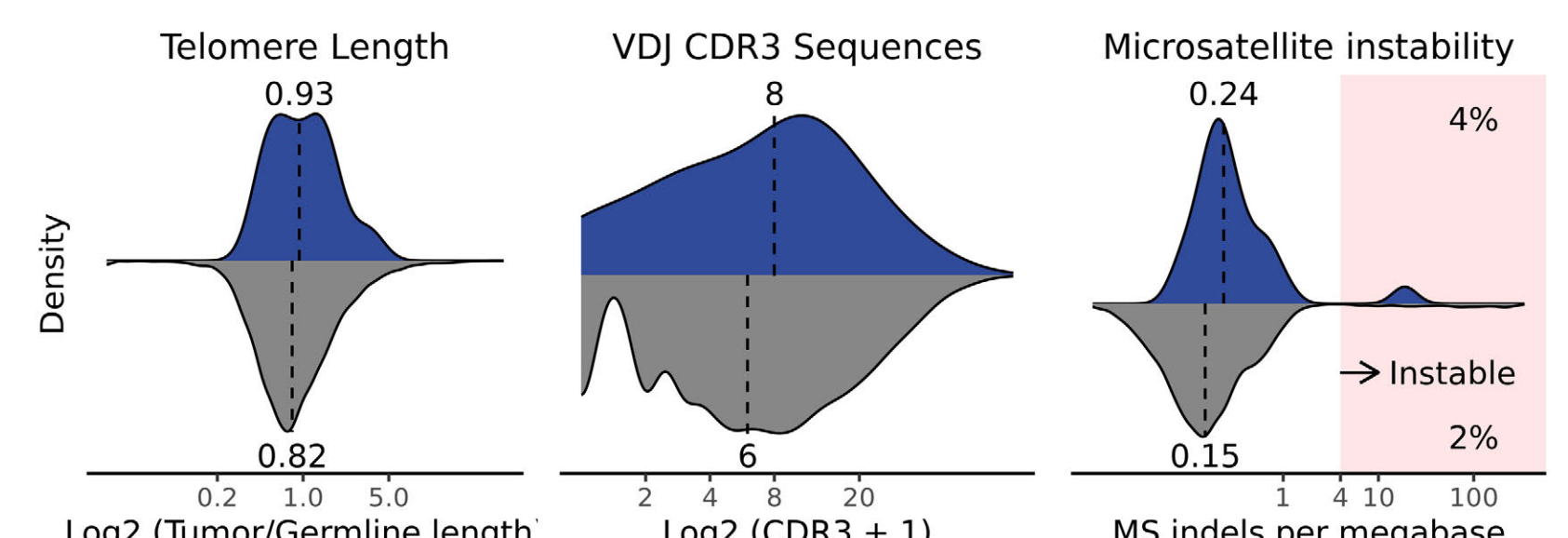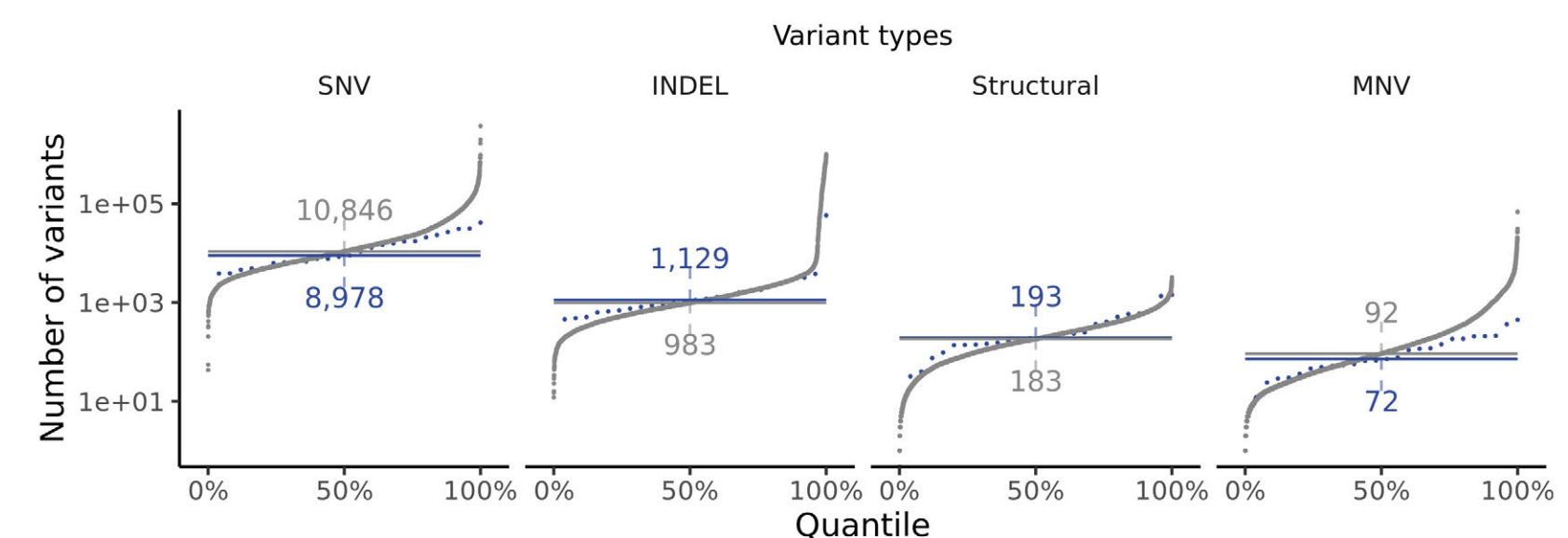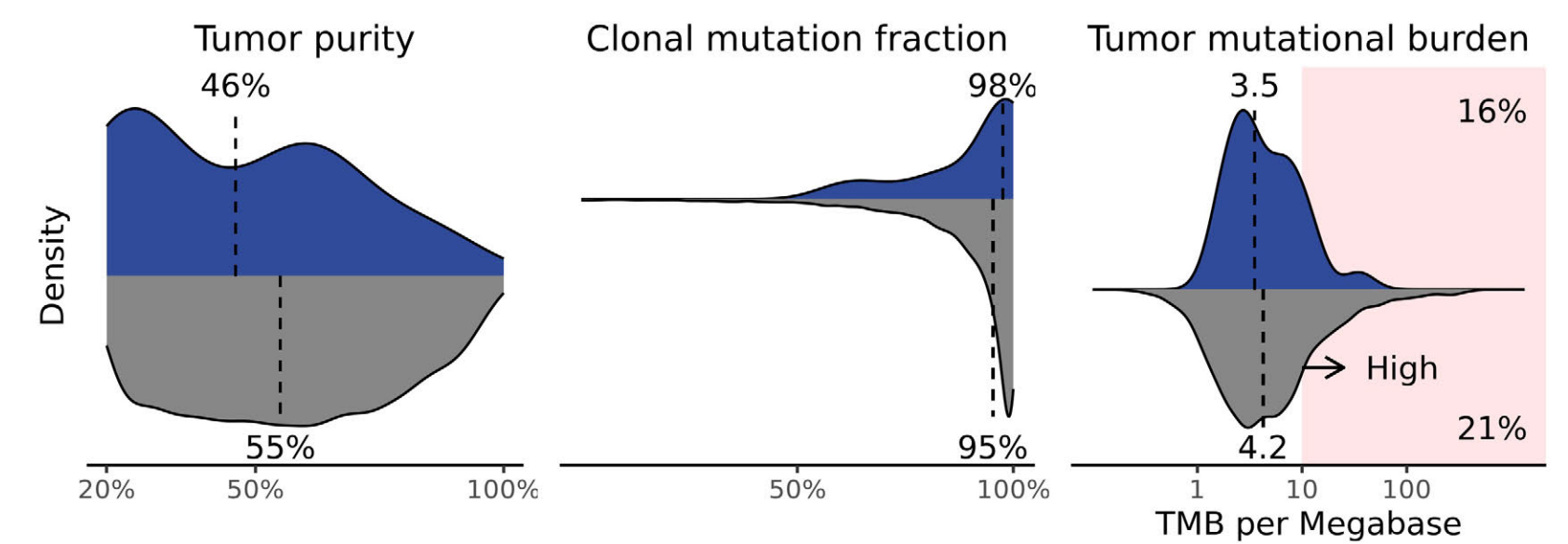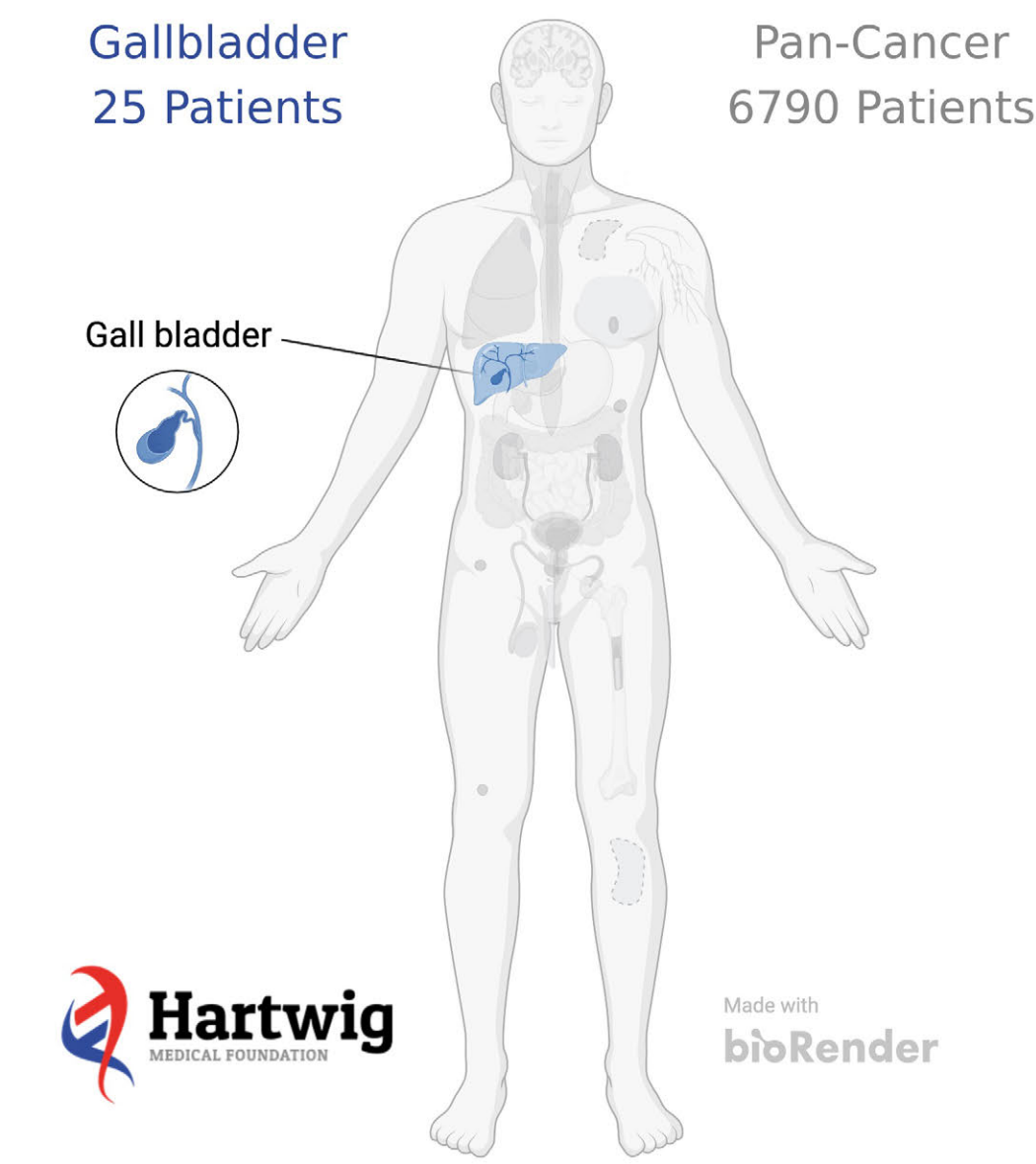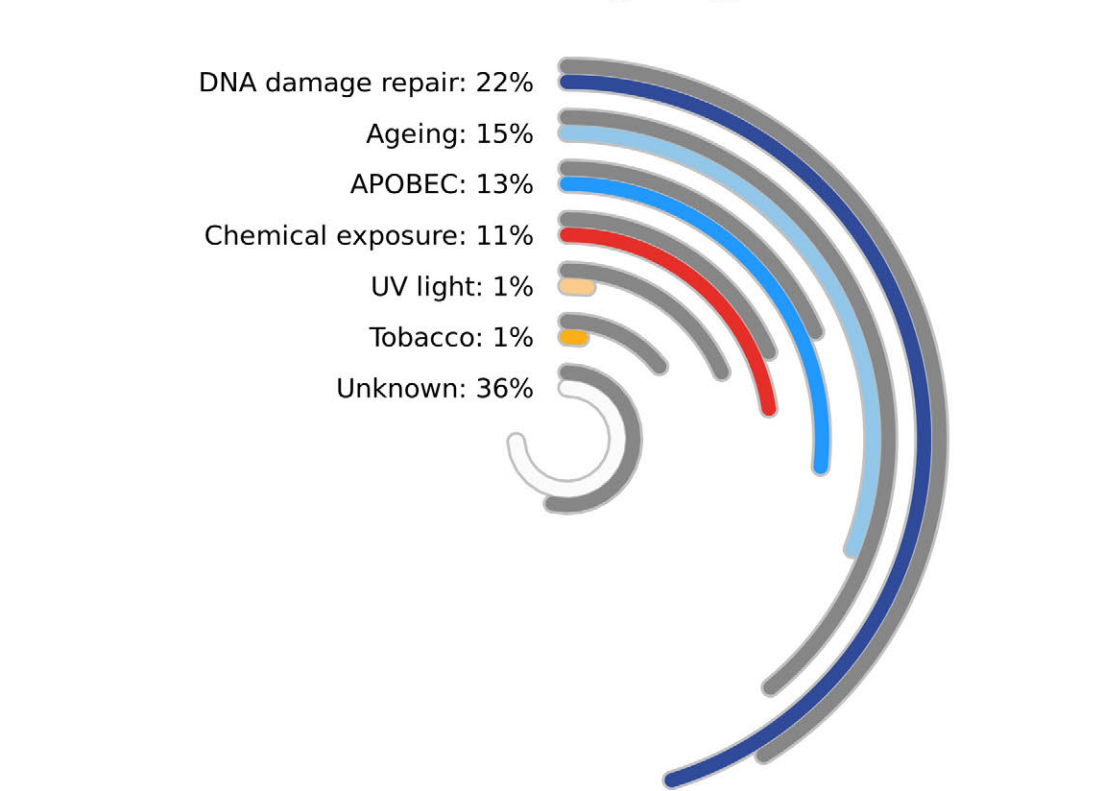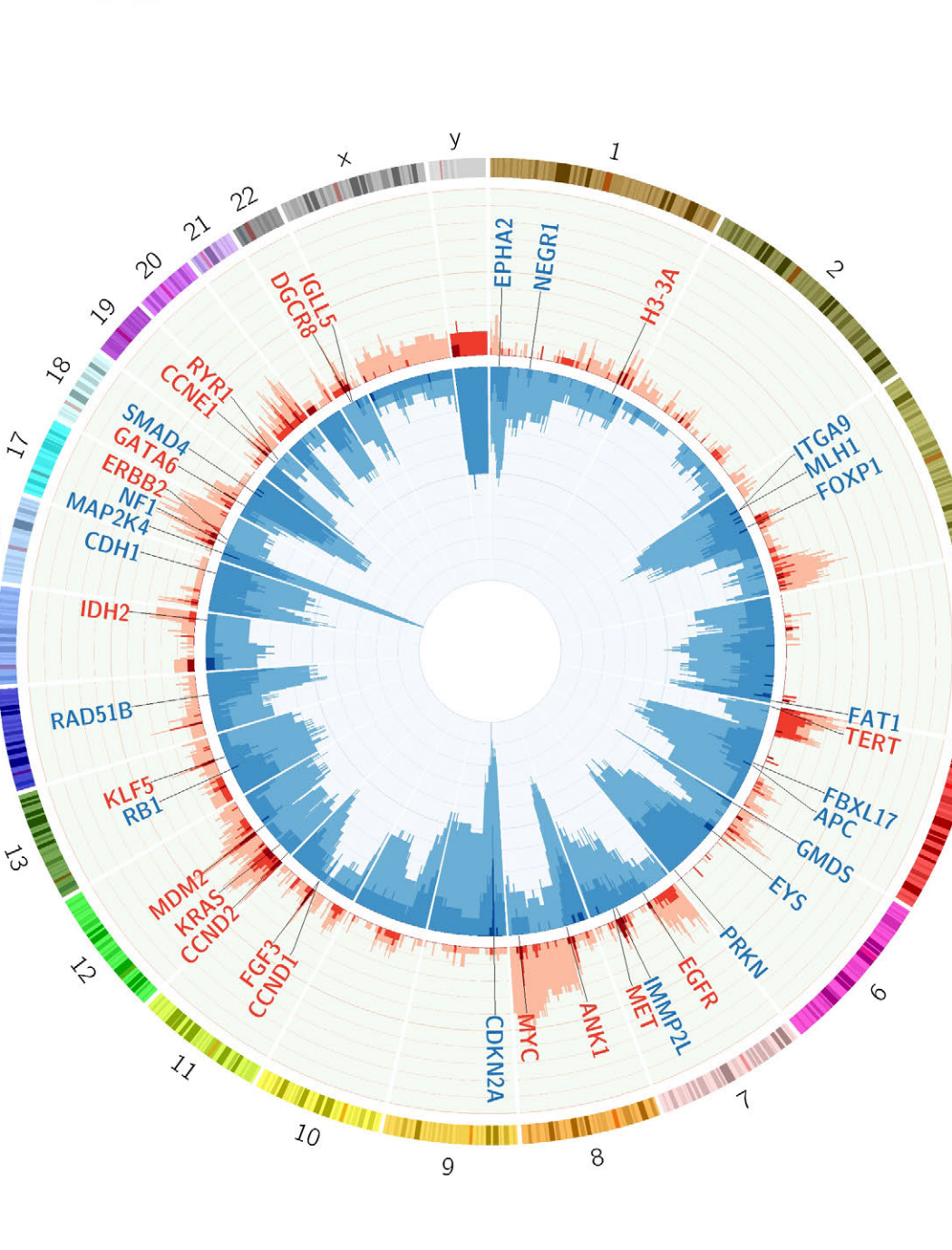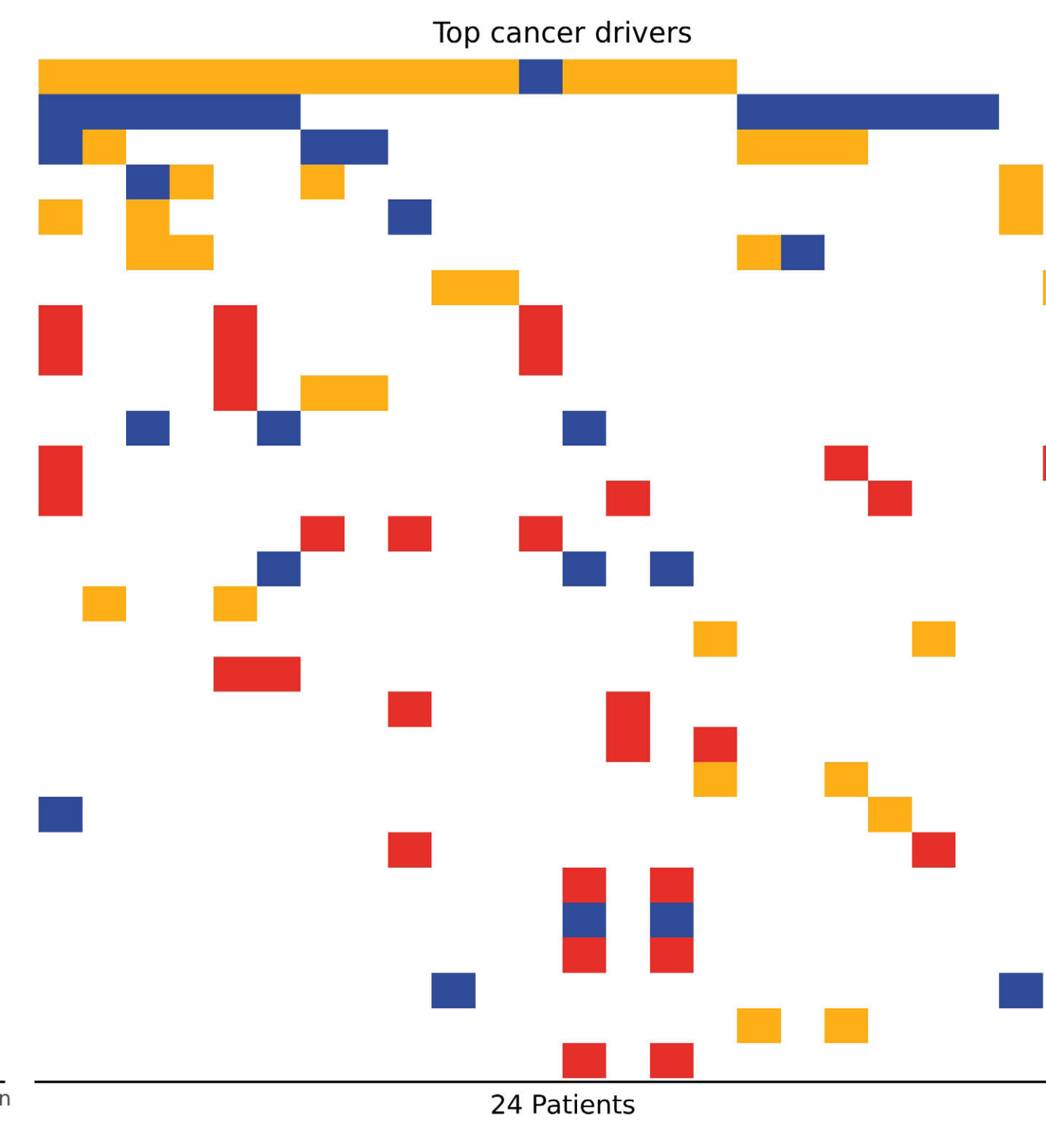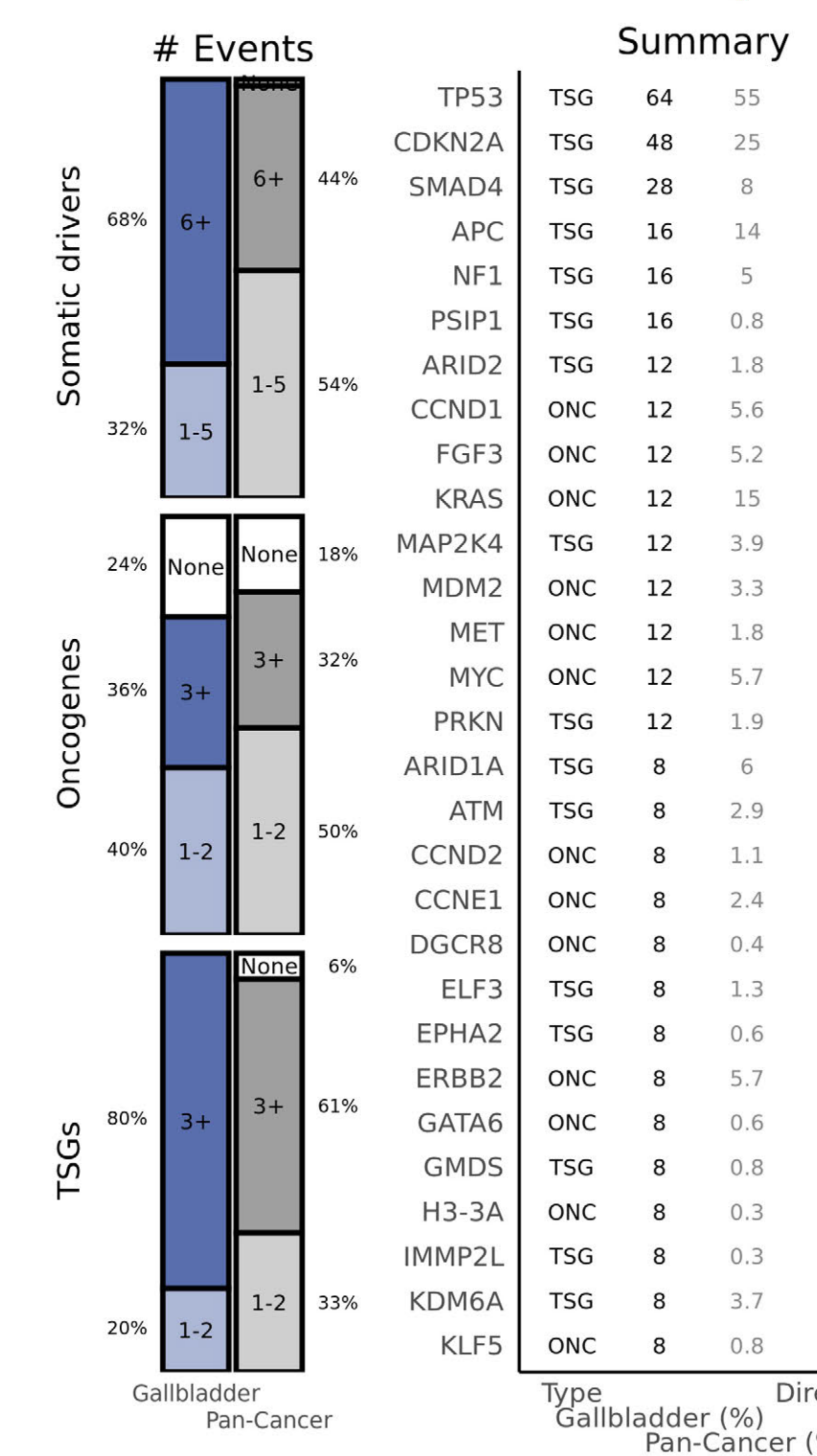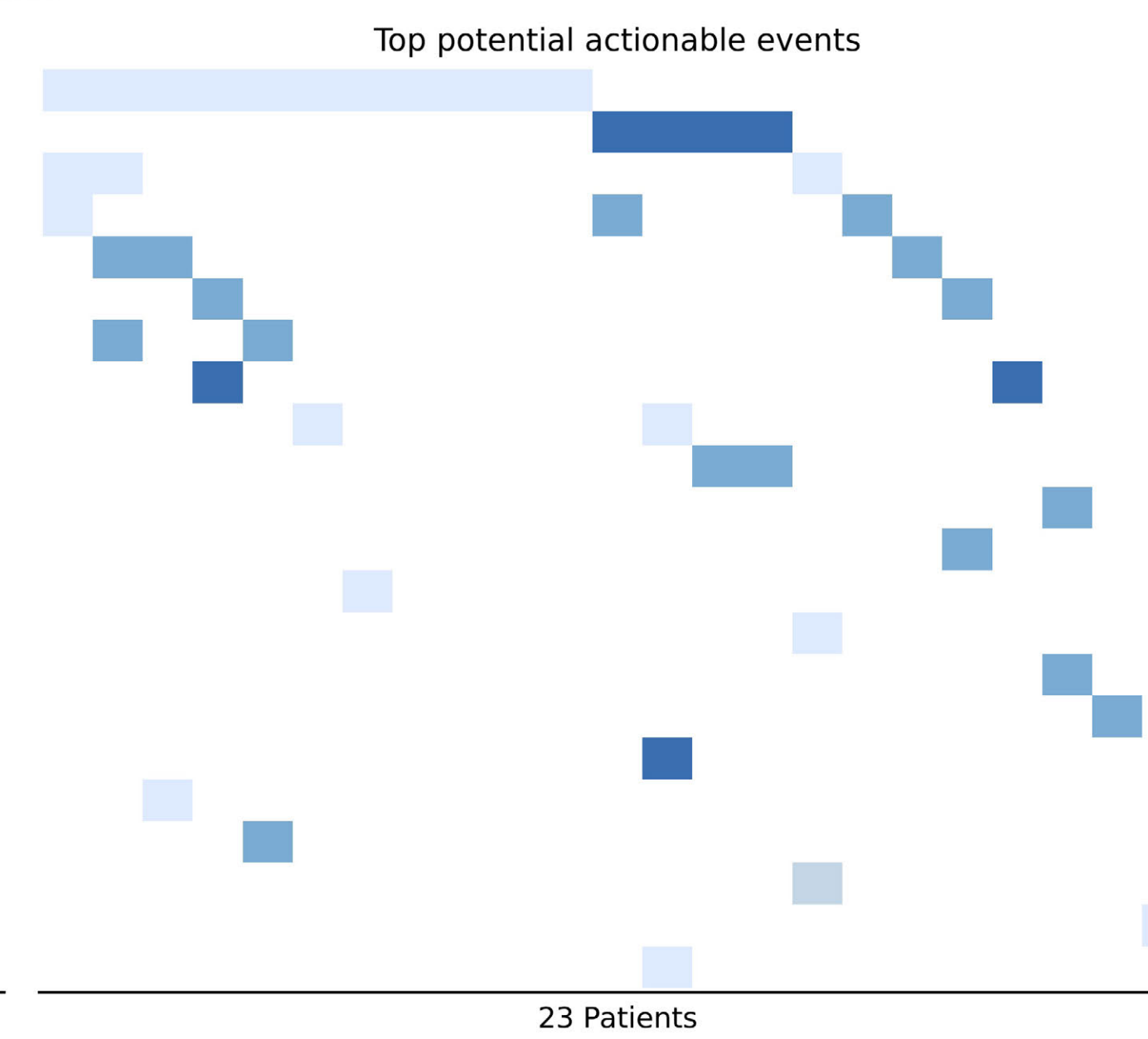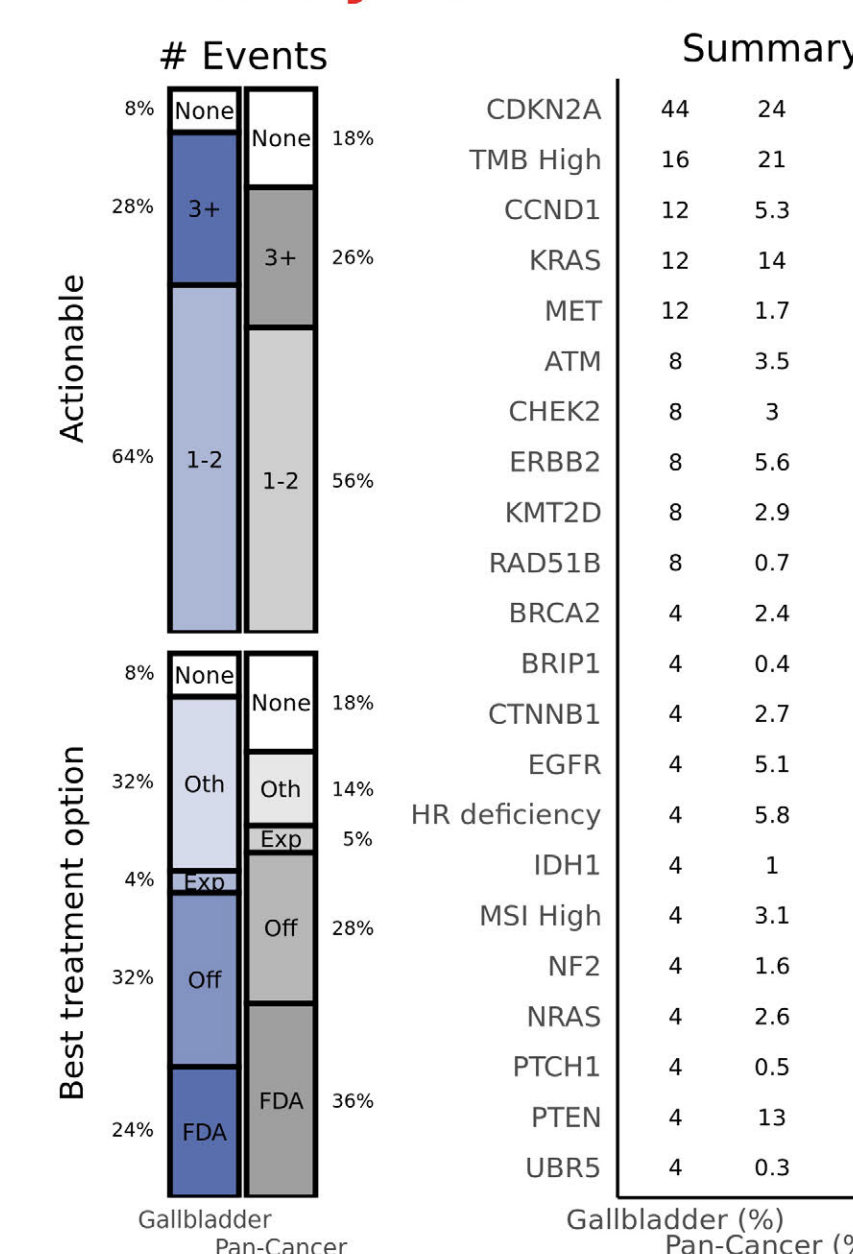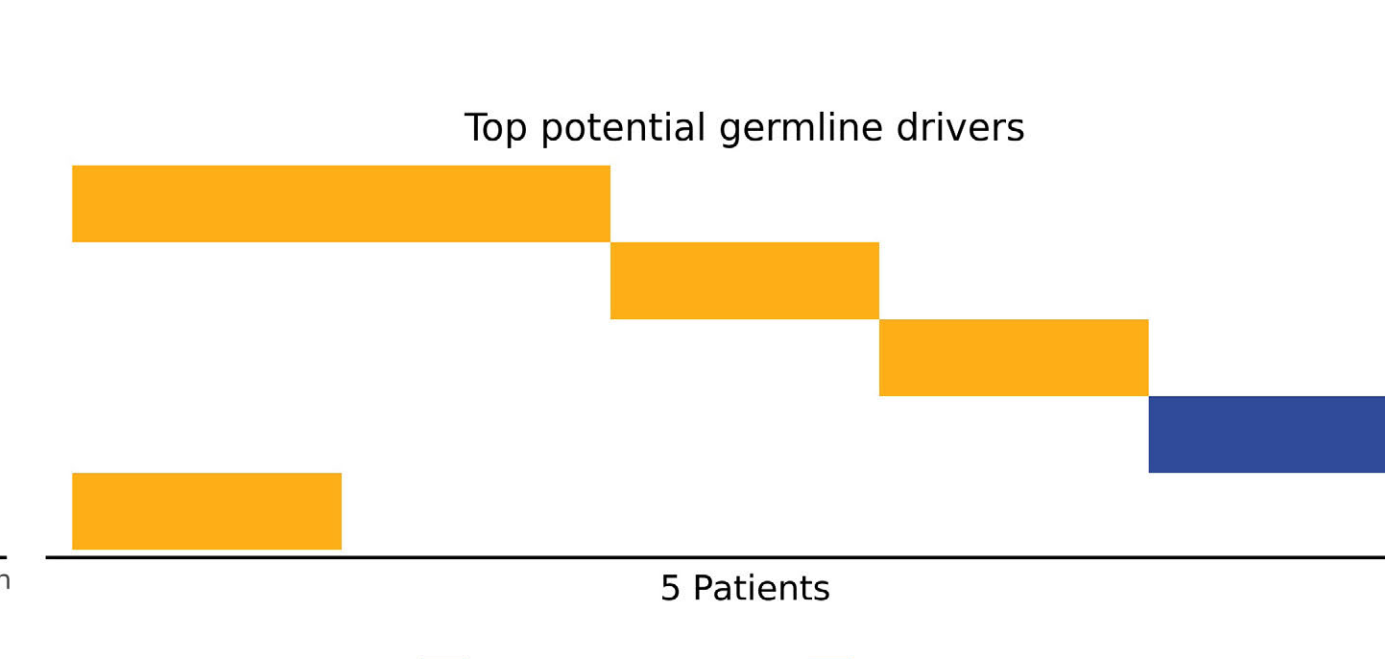** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Gallbladder Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 25 |
| RNASeq | 19 |
| Age, Sex | 20 |
| Biopsy site | 19 |
| Pretreatment | 19 |
| Treatment | 15 → |
| Response | 14 → |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | Post-biopsy | Responders |
|---|---|---|
| Chemo | 11 | 3 (27%) |
| Multiple | 1 | 1 (100%) |
| Targeted | 2 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 1 | 0 |
| Other | 1 | 0 |
| None or NA | 0 | |

## Processes Underlying Mutations

- DNA damage repair: 22%
- Ageing: 15%
- APOBEC: 13%
- Chemical exposure: 11%
- UV light: 1%
- Tobacco: 1%
- Unknown: 36%

Gallbladder
25 Patients

Pan-Cancer
6790 Patients

Gall bladder

Made with bioRender

## Tumor Characteristics

■ Gallbladder ■ Pan-Cancer

| | Gallbladder | Pan-Cancer |
|---|---|---|
| TMB High | 16% | 21% |
| MSI High | 4% | 2% |
| WGD | 68% | 56% |
| Diploid Proportion | 23% | 34% |
| GIE HLA LOH | 20% | 19% |
| GIE Overall | 24% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 4% | 6% |

## Mutational Landscape

### Tumor purity
46% / 55%

### Clonal mutation fraction
98% / 95%

### Tumor mutational burden
3.5 — 16% High
4.2 — 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 8,978 | 1,129 / 983 | 193 / 183 | 92 / 72 |

Number of variants / Quantile

### Telomere Length
0.93 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
8 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.24 — 4% Instable
0.15 — 2%
MS indels per megabase

### Mean genome ploidy
2.7 / 2.6

### Aneuploidy Score
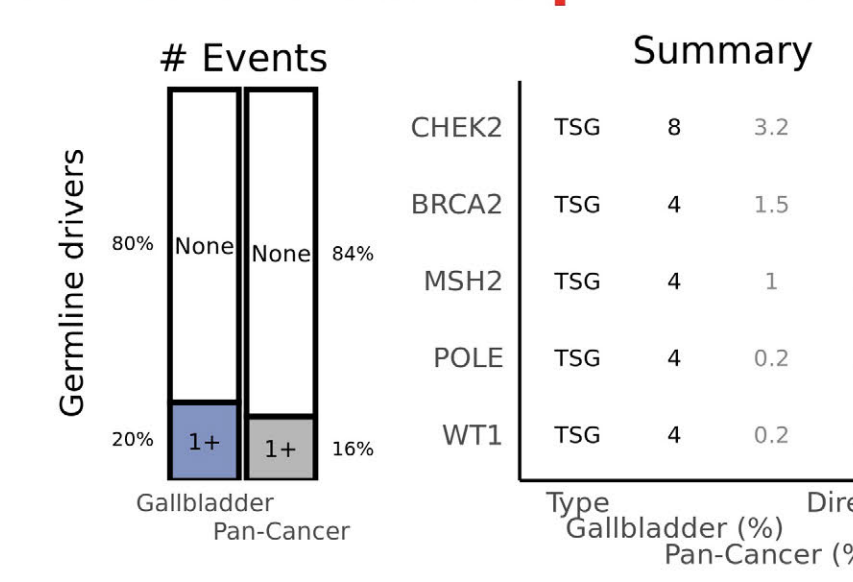19 / 16

### % Copy number alteration
60% / 54%

### % Genome LOH
32% / 24%
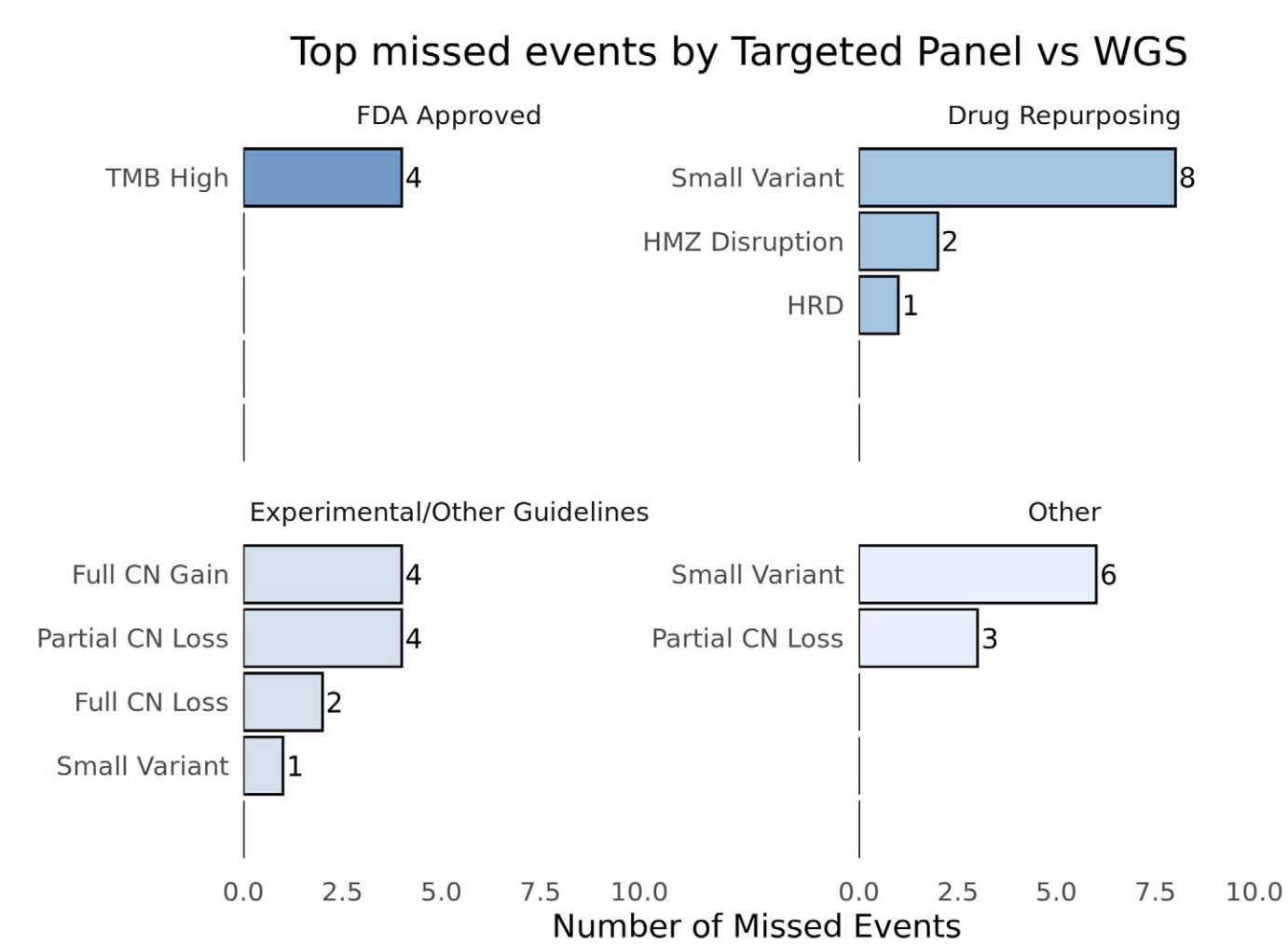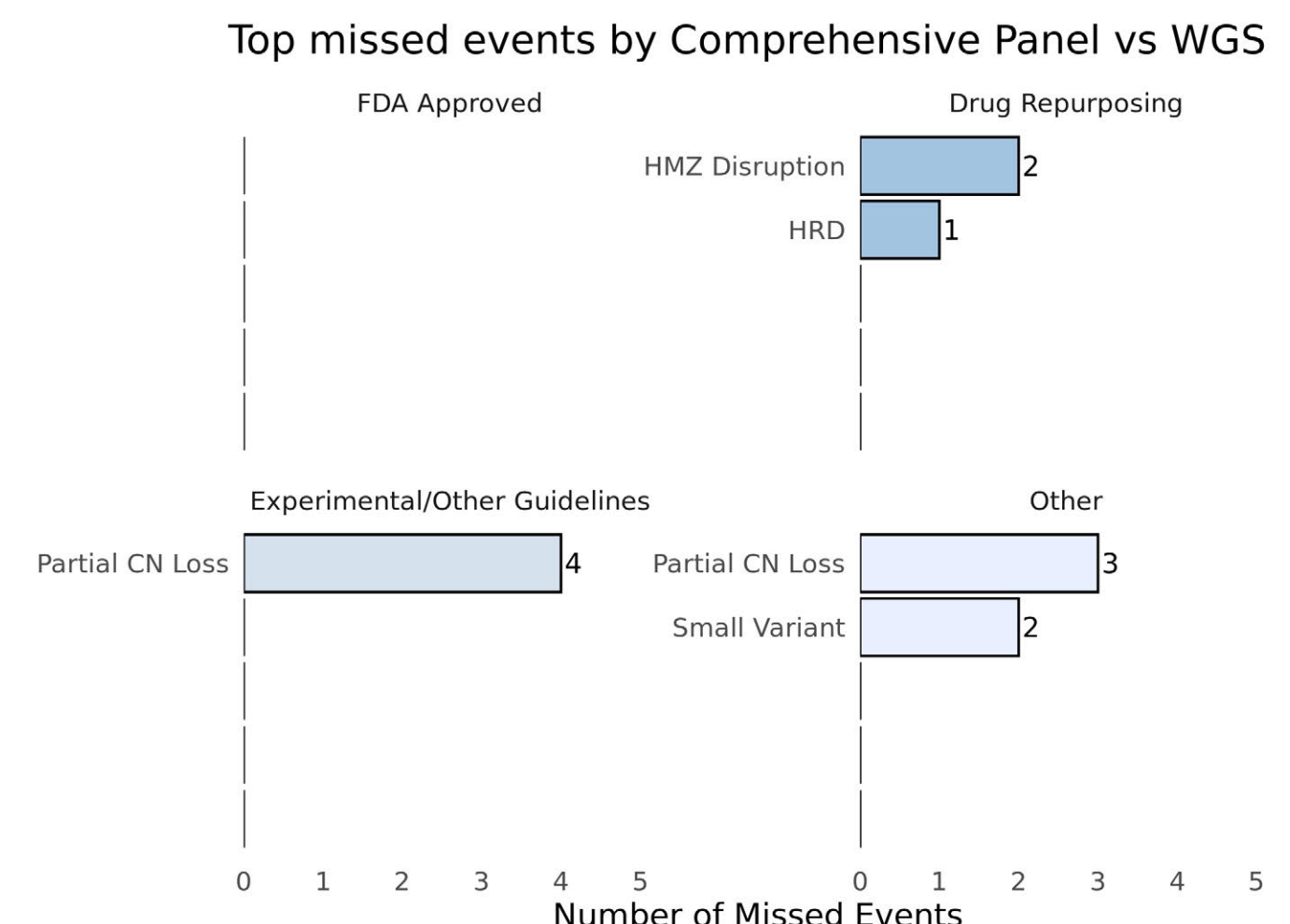
## Copy Number Alteration Profile

## Cancer Driver Landscape

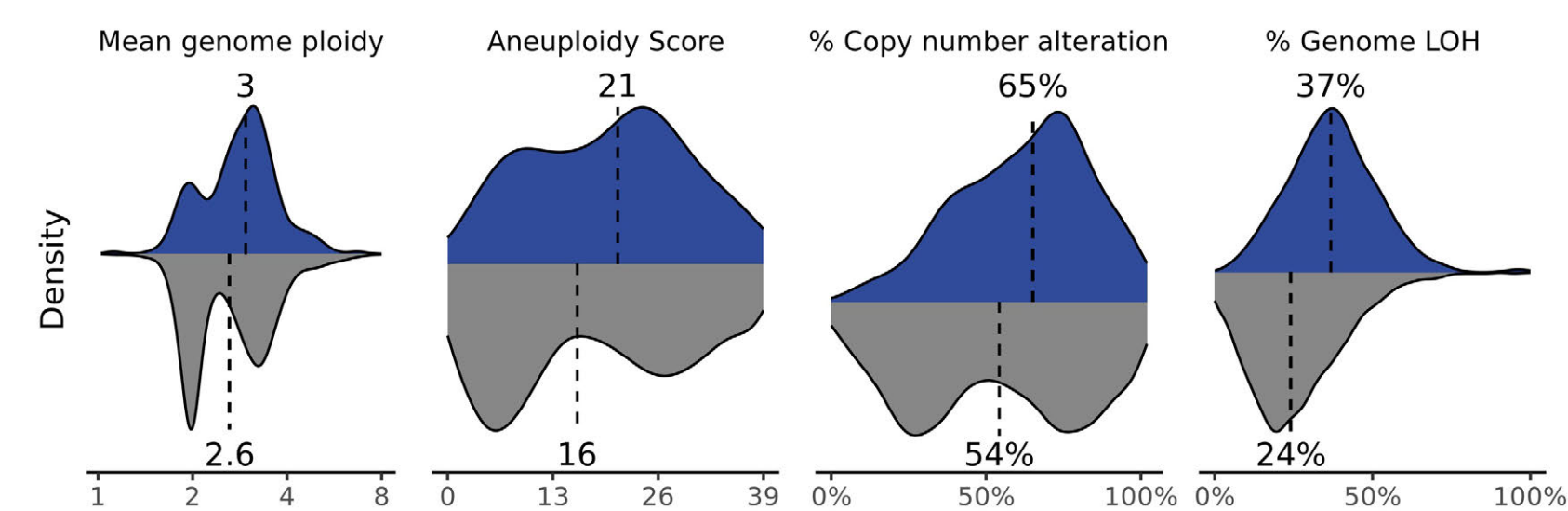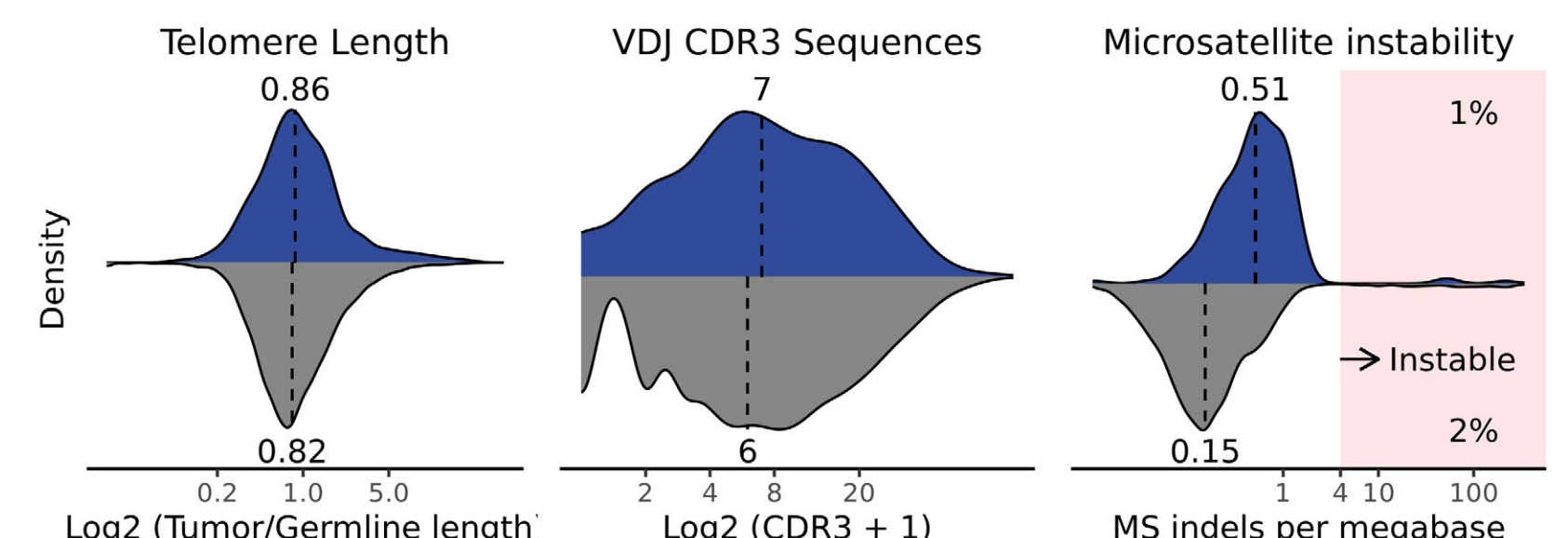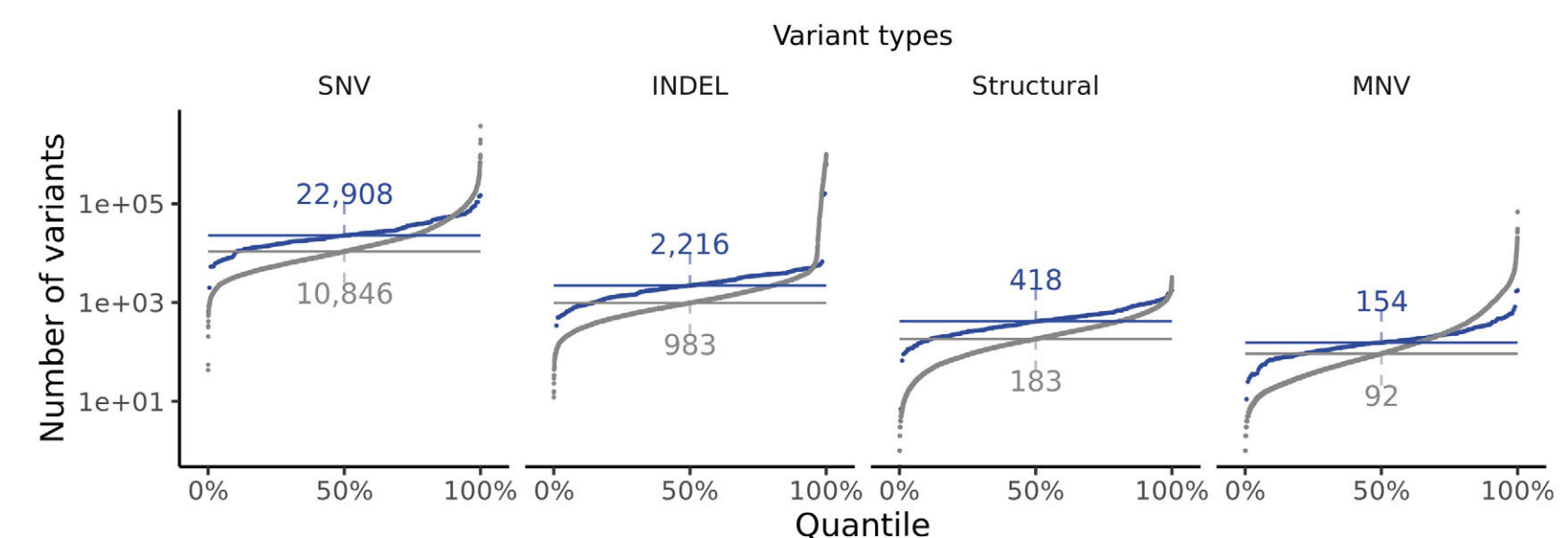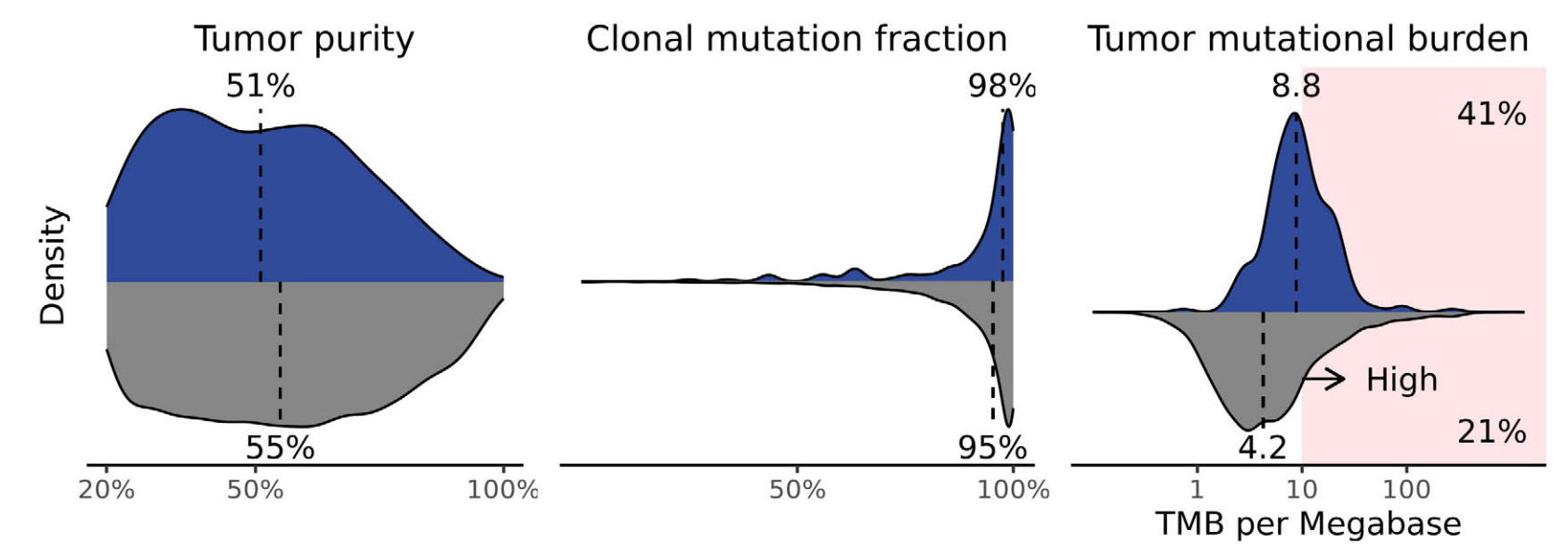### # Events / Summary — Top cancer drivers

**Somatic drivers** 68% / 44% (6+), 32% / 54% (1-5)
**Oncogenes** 24% / 18% (None), 36% / 32% (3+), 40% / 50% (1-2)
**TSGs** 80% / 61% (3+), 20% / 33% (1-2)

| Gene | Type | Gallbladder (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 64 | 55 | ▲ |
| CDKN2A | TSG | 48 | 25 | ▲ |
| SMAD4 | TSG | 28 | 8 | ▲ |
| APC | TSG | 16 | 14 | |
| NF1 | TSG | 16 | 5 | |
| PSIP1 | TSG | 16 | 0.8 | ▲ |
| ARID2 | TSG | 12 | 1.8 | ▲ |
| CCND1 | ONC | 12 | 5.6 | ▲ |
| FGF3 | ONC | 12 | 5.2 | ▲ |
| KRAS | ONC | 12 | 15 | |
| MAP2K4 | TSG | 12 | 3.9 | ▲ |
| MDM2 | ONC | 12 | 2.3 | ▲ |
| MET | ONC | 12 | 1.8 | ▲ |
| MYC | ONC | 12 | 5.7 | ▲ |
| PRKN | TSG | 12 | 1.9 | ▲ |
| ARID1A | TSG | 8 | 8 | ▲ |
| ATM | TSG | 8 | 2.9 | ▲ |
| CCND2 | ONC | 8 | 1.1 | ▲ |
| CCNE1 | ONC | 8 | 2.4 | ▲ |
| DGCR8 | ONC | 8 | 0.4 | ▲ |
| ELF3 | TSG | 8 | 1.3 | ▲ |
| EPHA2 | TSG | 8 | 0.6 | ▲ |
| ERBB2 | ONC | 8 | 5.7 | ▲ |
| GATA6 | ONC | 8 | 0.6 | ▲ |
| GMDS | ONC | 8 | 0.8 | ▲ |
| H3-3A | ONC | 8 | 0.3 | ▲ |
| IMMP2L | TSG | 8 | 0.3 | ▲ |
| KDM6A | TSG | 8 | 3.7 | ▲ |
| KLF5 | ONC | 8 | 0.3 | ▲ |

Top cancer drivers — 24 Patients

■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events / Summary — Top potential actionable events

**Actionable** 8% / 18% (None), 28% / 26% (3+), 64% / 56% (1-2)
**Best treatment option** 8% / 18% (None), 32% / 14% (Oth), 4% (Exp), 32% / 28% (Off), 24% / 36% (FDA)

| Gene | Gallbladder (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 44 | 24 | |
| TMB High | 16 | 21 | ▲ |
| CCND1 | 12 | 5.3 | ▲ |
| KRAS | 12 | 14 | |
| MET | 12 | 1.7 | ▲ |
| ATM | 8 | 3.5 | |
| CHEK2 | 8 | 3 | ▲ |
| ERBB2 | 8 | 5.6 | |
| KMT2D | 8 | 2.9 | ▲ |
| RAD51B | 8 | 0.7 | ▲ |
| BRCA2 | 4 | 2.4 | |
| BRIP1 | 4 | 0.4 | ▲ |
| CTNNB1 | 4 | 2.7 | |
| EGFR | 4 | 5.1 | |
| HR deficiency | 4 | 5.8 | |
| IDH1 | 4 | 1 | ▲ |
| MSI High | 4 | 3.1 | |
| NF2 | 4 | 1.6 | |
| NRAS | 4 | 2.6 | |
| PTCH1 | 4 | 0.5 | ▲ |
| PTEN | 4 | 13 | ▼ |
| UBR5 | 4 | 0.3 | ▲ |

Top potential actionable events — 23 Patients

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events / Summary
**Germline drivers** 80% / 84% (None), 20% / 16% (1+)

| Gene | Type | Gallbladder (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 8 | 3.2 | |
| BRCA2 | TSG | 4 | 1.5 | |
| MSH2 | TSG | 4 | 1 | ▲ |
| POLE | TSG | 4 | 0.2 | ▲ |
| WT1 | TSG | 4 | 0.2 | ▲ |

Top potential germline drivers — 5 Patients

■ STRUCTURAL_VARIANT ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing ■ Other ■ None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA Approved | Drug Repurposing | Other | None |
|---|---|---|---|---|
| WGS | 6 | 8 | 4 | 6 / 1 |
| Comprehensive 521 gene panel | 6 | 8 | 3 | 6 / 2 |
| Targeted 50 gene panel | 3 | 7 | 7 | 8 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.28 | 0.72 | 0.48 | 0.8 | 2.3 |
| Comprehensive 521 gene panel | 0.28 | 0.6 | 0.32 | 0.6 | 1.8 |
| Targeted 50 gene panel | 0.28 | 0.44 | | | 0.9 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved** — Partial CN Loss: 4
**Drug Repurposing** — HMZ Disruption: 2, HRD: 1
**Experimental/Other Guidelines** — Partial CN Loss: 4
**Other** — Partial CN Loss: 3, Small Variant: 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved** — TMB High: 4
**Drug Repurposing** — Small Variant: 8, HMZ Disruption: 2, HRD: 1
**Experimental/Other Guidelines** — Full CN Gain: 4, Partial CN Loss: 4, Full CN Loss: 2, Small Variant: 1
**Other** — Small Variant: 6, Partial CN Loss: 3

Number of Missed Events

# The Genomic And Actionability Landscape Of Esophageal Carcinoma

## Cohort Metadata

### Data availability
Number of patients with data

| | |
|---|---|
| WGS | 204 |
| RNASeq | 145 |
| Age, Sex | 140 |
| Biopsy site | 140 |
| Pretreatment | 128 |
| Treatment | 105 → |
| Response | 88 → |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | |
|---|---|
| Chemo | 62 / 20 (32%) |
| Multiple | 27 / 13 (48%) |
| Targeted | 1 / 0 |
| Hormonal | 0 / 0 |
| Immuno | 1 / 0 |
| Radio | 18 / 5 (28%) |
| Other | 0 / 0 |
| None or NA | 0 / 0 |

## Processes Underlying Mutations

- Chemical exposure: 13%
- DNA damage repair: 12%
- APOBEC: 9%
- Ageing: 6%
- Tobacco: 3%
- UV light: 3%
- Unknown: 55%

## Tumor Characteristics

Gastroesophageal / Pan-Cancer

| | Gastroesophageal | Pan-Cancer |
|---|---|---|
| TMB High | 41% | 21% |
| MSI High | 1% | 2% |
| WGD | 79% | 56% |
| Diploid Proportion | 19% | 34% |
| GIE HLA LOH | 38% | 19% |
| GIE Overall | 43% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 1% | 6% |

### Gastroesophageal
204 Patients

### Pan-Cancer
6790 Patients

Gastroesophageal

## Mutational Landscape

### Tumor purity
51% / 55%

### Clonal mutation fraction
98% / 95%

### Tumor mutational burden
8.8 / 4.2 — High 41% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 22,908 / 10,846 | 2,216 / 983 | 418 / 183 | 154 / 92 |

Number of variants — Quantile

### Telomere Length
0.86 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
7 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.51 / 0.15 — Instable 1% / 2%
MS indels per megabase

### Mean genome ploidy
3 / 2.6

### Aneuploidy Score
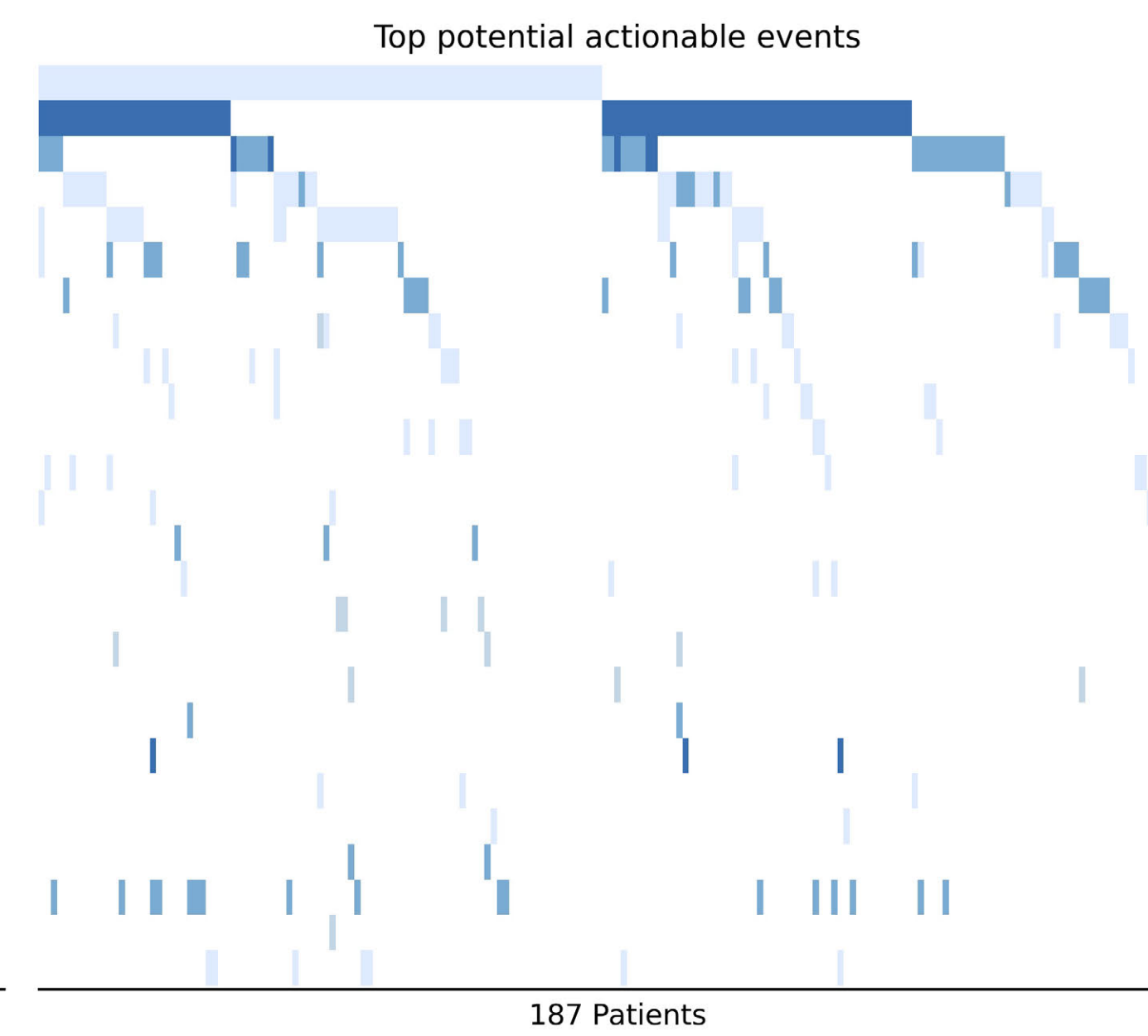21 / 16
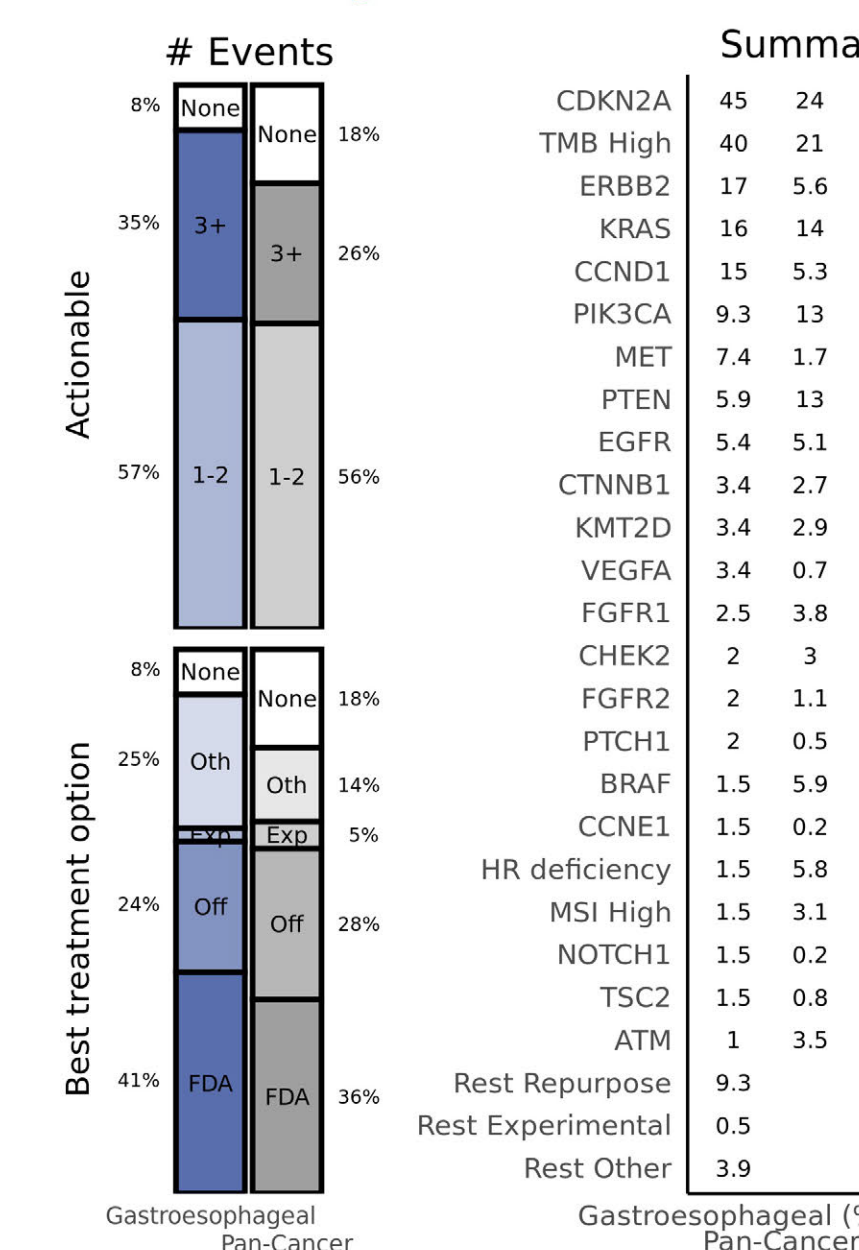
### % Copy number alteration
65% / 54%

### % Genome LOH
37% / 24%
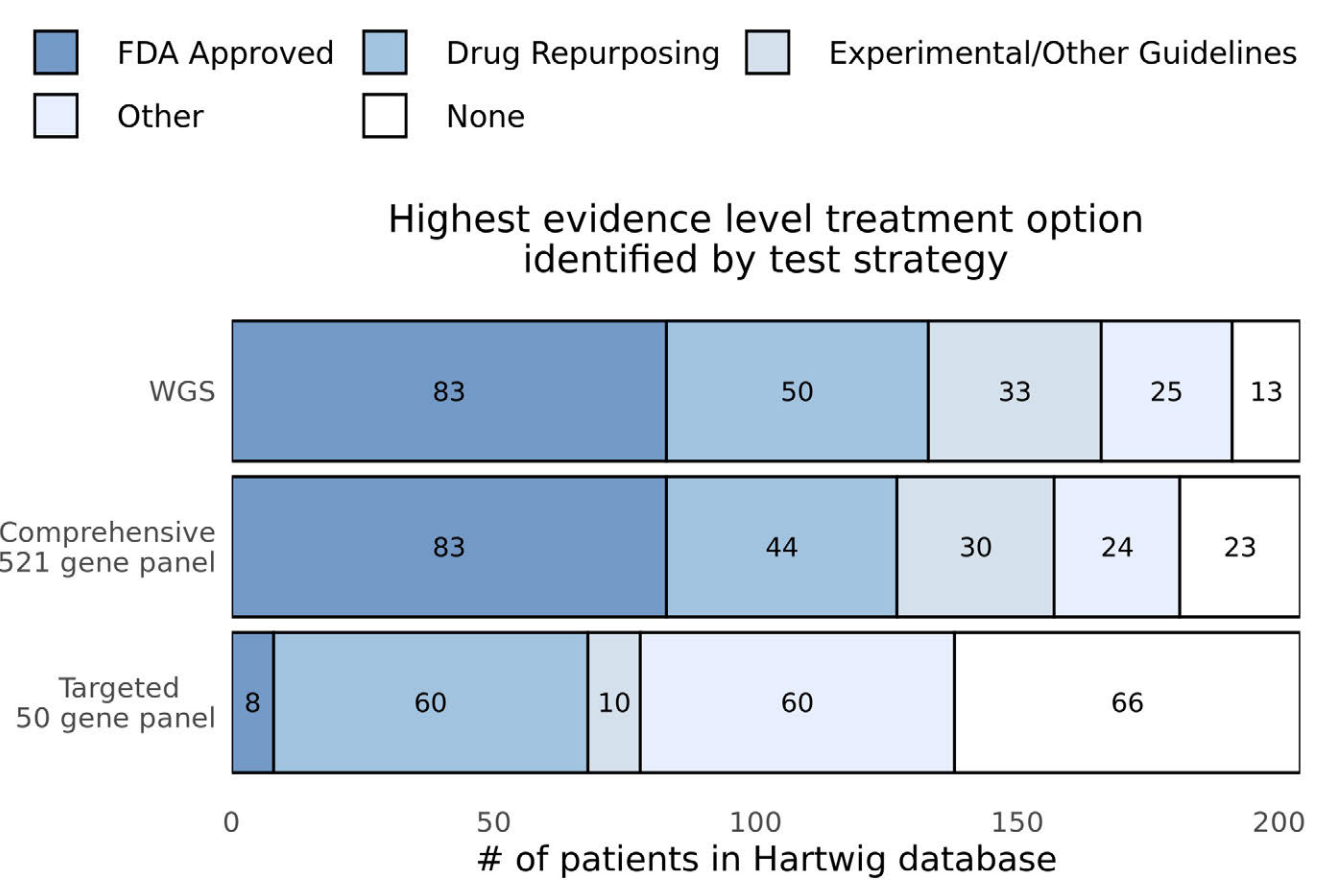
## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events

Somatic drivers: 79% 6+ / 21% 1-5
Oncogenes: 14% None / 46% 3+ / 40% 1-2
TSGs: 88% 3+ / 12% 1-2

### Summary

| | Type | Gastroesophageal (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 89 | 55 | ▲ |
| FHIT | TSG | 49 | 4.3 | ▲ |
| CDKN2A | TSG | 45 | 25 | ▲ |
| DMD | TSG | 35 | 3.5 | ▲ |
| ERBB2 | ONC | 17 | 5.7 | ▲ |
| KRAS | ONC | 16 | 15 | |
| CCND1 | ONC | 16 | 5.6 | ▲ |
| FGF3 | ONC | 16 | 5.2 | ▲ |
| ARID1A | TSG | 14 | 8 | |
| SMAD4 | TSG | 14 | 8 | |
| MYC | ONC | 13 | 5.7 | ▲ |
| CCNE1 | ONC | 11 | 2.4 | ▲ |
| GMDS | TSG | 9.8 | 0.8 | ▲ |
| APC | TSG | 9.3 | 14 | |
| CCSER1 | TSG | 9.3 | 1.6 | ▲ |
| PIK3CA | ONC | 9.3 | 13 | |
| GATA6 | ONC | 8.3 | 0.6 | ▲ |
| PTPRD | TSG | 8.3 | 3 | |
| STS | TSG | 8.3 | 1.6 | ▲ |
| KDM6A | TSG | 7.8 | 3.7 | |
| LRP1B | TSG | 7.4 | 2.1 | ▲ |
| MET | ONC | 7.4 | 1.8 | ▲ |
| SMARCA4 | TSG | 7.4 | 2.5 | |
| TGFBR2 | TSG | 7.4 | 2.7 | |
| CDK6 | ONC | 6.9 | 1.6 | ▲ |
| CSMD1 | TSG | 6.9 | 1.2 | ▲ |
| PDE4D | TSG | 6.9 | 1 | ▲ |
| MACROD2 | TSG | 6.4 | 1.5 | ▲ |
| RB1 | TSG | 6.4 | 11 | |

### Top cancer drivers
202 Patients

Legend: AMPLIFICATION / DELETION / MUTATION

## Potentially Actionable Events

### # Events

Actionable: 8% None / 35% 3+ / 57% 1-2
Best treatment option: 8% None / 25% Oth / 24% Off / 41% FDA

### Summary

| | Gastroesophageal (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 45 | 24 | |
| TMB High | 40 | 21 | |
| ERBB2 | 17 | 5.6 | |
| KRAS | 16 | 14 | |
| CCND1 | 15 | 5.3 | |
| PIK3CA | 9.3 | 13 | |
| MET | 7.4 | 1.7 | ▲ |
| PTEN | 5.9 | 13 | ▼ |
| EGFR | 5.4 | 5.1 | |
| CTNNB1 | 3.4 | 2.7 | |
| KMT2D | 3.4 | 2.9 | |
| VEGFA | 3.4 | 0.7 | ▲ |
| FGFR1 | 2.5 | 3.8 | |
| CHEK2 | 2 | 3 | |
| FGFR2 | 2 | 1.1 | |
| PTCH1 | 2 | 0.5 | ▲ |
| BRAF | 1.5 | 5.9 | ▼ |
| CCNE1 | 1.5 | 0.2 | |
| HR deficiency | 1.5 | 5.8 | ▼ |
| MSI High | 1.5 | 3.1 | |
| NOTCH1 | 1.5 | 0.2 | ▲ |
| TSC2 | 1.5 | 0.8 | |
| ATM | 1 | 3.5 | ▼ |
| Rest Repurpose | 9.3 | | |
| Rest Experimental | 0.5 | | |
| Rest Other | 3.9 | | |

### Top potential actionable events
187 Patients

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

### # Events
Germline drivers: 87% None / 13% 1+

### Summary

| | Type | Gastroesophageal (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 2 | 3.2 | |
| MUTYH | TSG | 2 | 1.9 | |
| MITF | ONC | 1.5 | 0.7 | |
| SDHA | TSG | 1.5 | 0.5 | |
| ATM | TSG | 1 | 1 | |
| BRCA2 | TSG | 1 | 1.5 | |
| BRCA1 | TSG | 0.5 | 1.1 | |
| FLCN | TSG | 0.5 | 0.1 | ▲ |
| MEN1 | TSG | 0.5 | 0.1 | ▲ |

### Top potential germline drivers
21 Patients

Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Other / Experimental/Other Guidelines / None

### Highest evidence level treatment option identified by test strategy

| | | | | | |
|---|---|---|---|---|---|
| WGS | 83 | 50 | 33 | 25 | 13 |
| Comprehensive 521 gene panel | 83 | 44 | 30 | 24 | 23 |
| Targeted 50 gene panel | 8 | 60 | 10 | 60 | 66 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.44 | 0.76 | 0.47 | 0.88 | 2.5 |
| Comprehensive 521 gene panel | 0.44 | 0.69 | 0.36 | 0.74 | 2.2 |
| Targeted 50 gene panel | 0.36 | 0.57 | | | 1 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved / Drug Repurposing
- Fusion — 6
- Partial CN Loss — 6
- HRD — 3

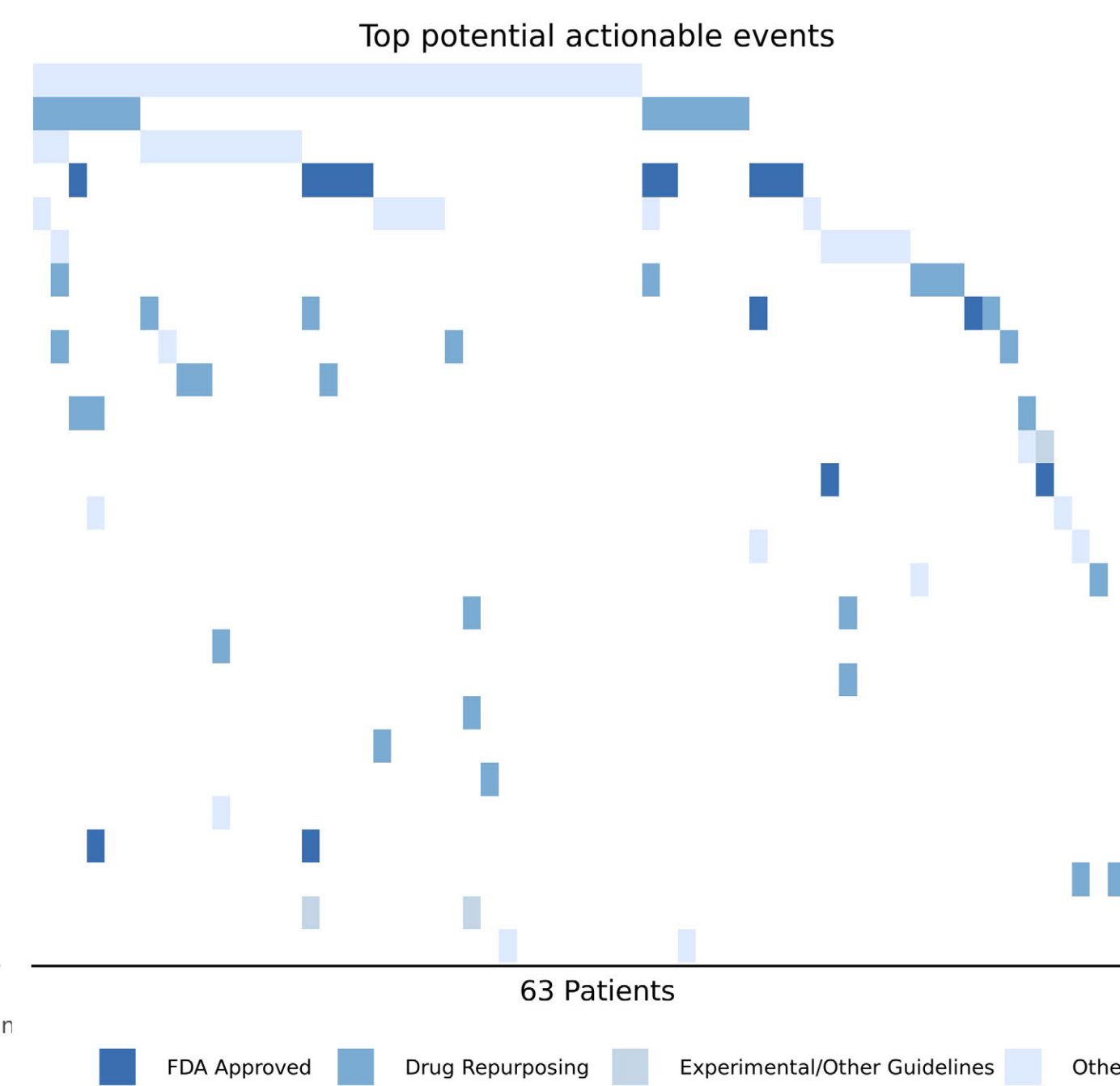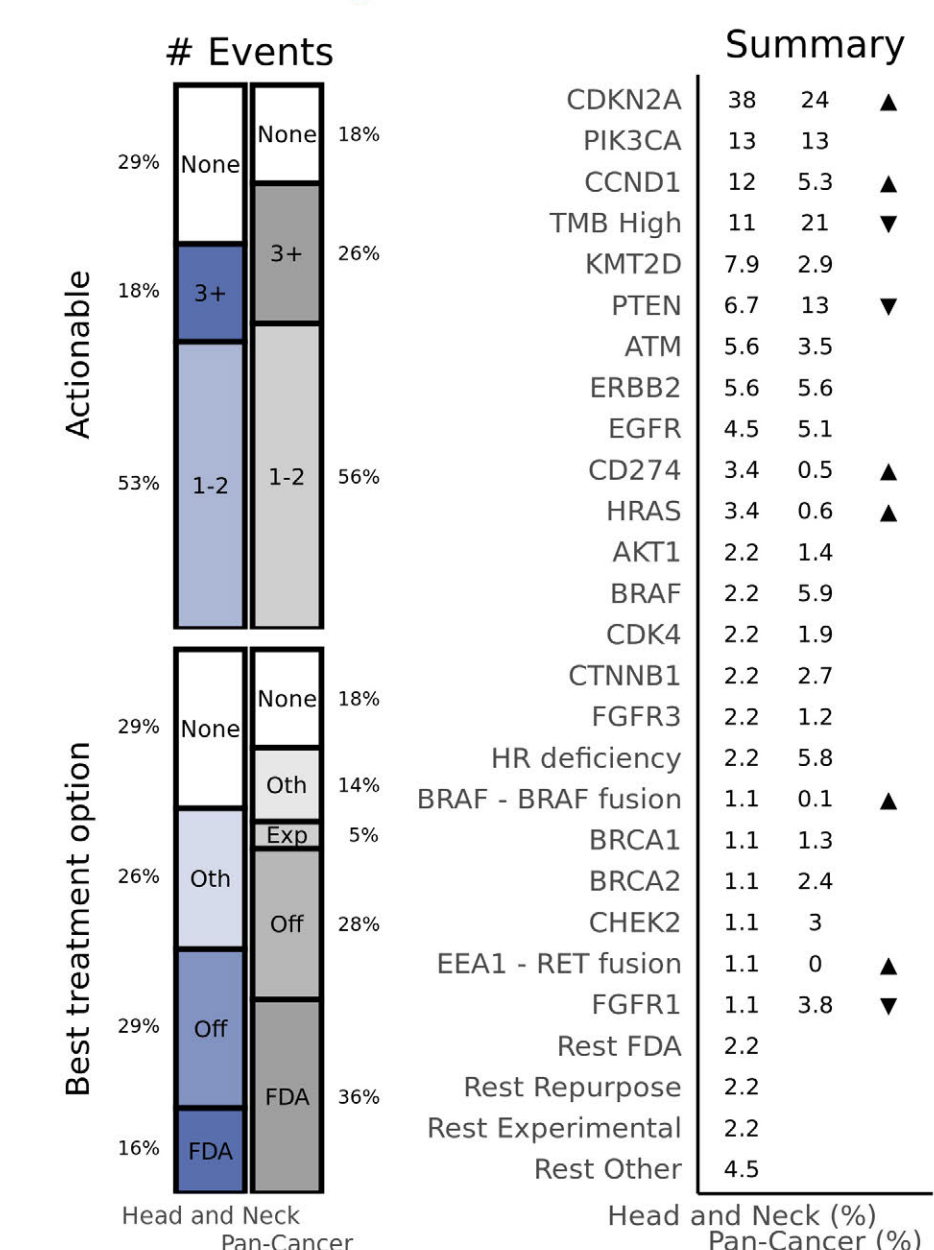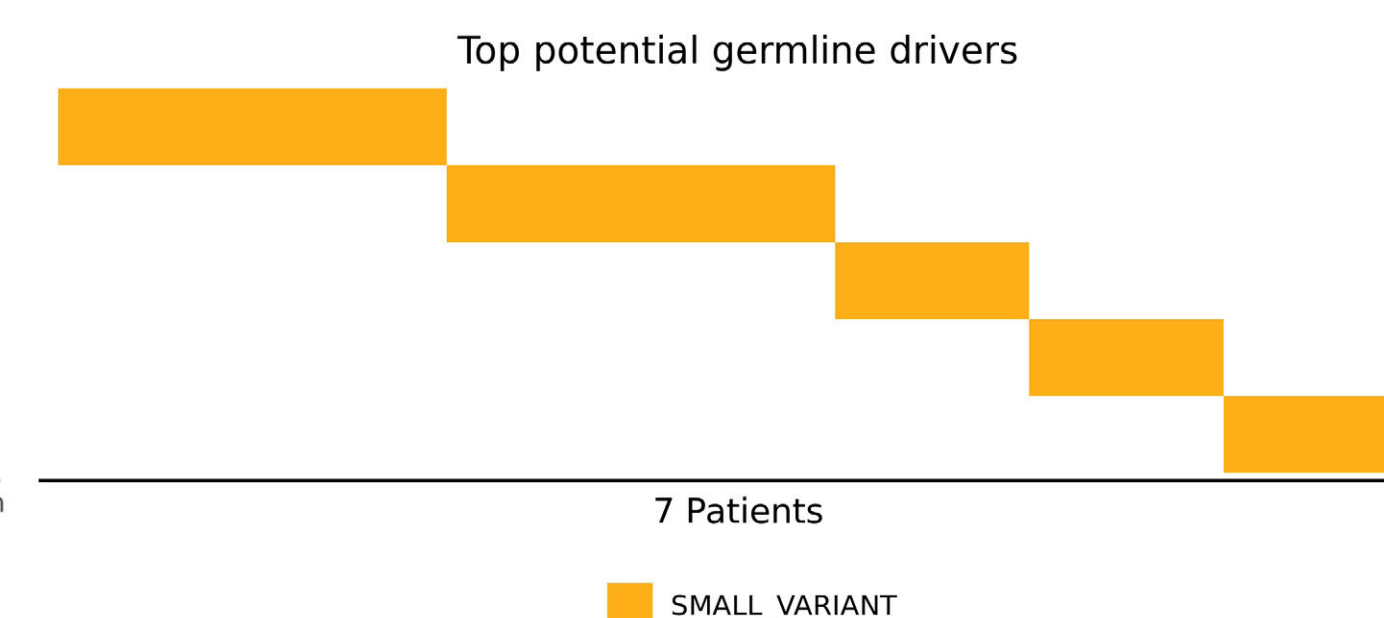Experimental/Other Guidelines
- Partial CN Loss — 17
- Full CN Gain — 2
- Fusion — 1
- Partial CN Gain — 1

Other
- Partial CN Loss — 22
- HMZ Disruption — 4
- Full CN Loss — 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved
- TMB High — 81

Drug Repurposing
- Small Variant — 65
- Fusion — 6
- Partial CN Loss — 6
- HRD — 3
- Splice Site — 2

Experimental/Other Guidelines
- Full CN Gain — 54
- Partial CN Loss — 17
- Small Variant — 3
- Full CN Loss — 2
- Partial CN Gain — 2

Other
- Small Variant — 26
- Partial CN Loss — 22
- HMZ Disruption — 4
- Splice Site — 4
- Full CN Gain — 3

Number of Missed Events

# The Genomic And Actionability Landscape Of Head And Neck Cancer

**Hartwig** MEDICAL FOUNDATION

Website: https://www.hartwigmedicalfoundation.nl
Tools: https://github.com/hartwigmedical/hmftools
Database: https://www.hartwigmedicalfoundation.nl/en/data/database/

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 89 |
| RNASeq | 53 |
| Age, Sex | 59 |
| Biopsy site | 57 |
| Pretreatment | 47 |
| Treatment | 38 → |
| Response | 29 → |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| Treatment | Count | Responders |
|---|---|---|
| Chemo | 8 | 2 (25%) |
| Multiple | 9 | 4 (44%) |
| Targeted | 3 | 0 |
| Hormonal | 4 | 0 |
| Immuno | 5 | 1 (20%) |
| Radio | 5 | 1 (20%) |
| Other | 0 | |
| None or NA | 0 | |

## Tumor Characteristics

■ Head and Neck ■ Pan-Cancer

| | Head and Neck | Pan-Cancer |
|---|---|---|
| TMB High | 12% | 21% |
| MSI High | 1% | 2% |
| WGD | 37% | 56% |
| Diploid Proportion | 49% | 34% |
| GIE HLA LOH | 21% | 19% |
| GIE Overall | 34% | 26% |
| Viral Insertions | 24% | 3% |
| HRD | 2% | 6% |

## Mutational Landscape

### Tumor purity
56% / 55%

### Clonal mutation fraction
94% / 95%

### Tumor mutational burden
3.1 / 4.2 — 12% High / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 7,812 | 983 / 905 | 183 / 141 | 94 / 92 |

Number of variants — Quantile

### Telomere Length
0.72 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
6 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.13 / 0.15 — 1% Instable / 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
8 / 16

### % Copy number alteration
35% / 54%

### % Genome LOH
23% / 24%

## Processes Underlying Mutations

| Process | % |
|---|---|
| APOBEC | 22% |
| Chemical exposure | 15% |
| DNA damage repair | 14% |
| UV light | 10% |
| Ageing | 7% |
| Tobacco | 3% |
| Unknown | 28% |

**Head and Neck** — 89 Patients
**Pan-Cancer** — 6790 Patients

Head and Neck

Made with bioRender

## Copy Number Alteration Profile

Genes labeled: CASZ1, ADAM30, SMAD4, TYMS, ERBB3, NF1, MAPK1, TP53, MDM2, CDK4, SLC01B1, FGF3, CCND1, CD44, ATXN, ARID1B, PARD3, CDKN2A, PTPRD, CD274, JAK2, MYC, FGFR1, AJNK1, CSM01, EGFR, CTNNA1, TERT, FAT1, LINC00290, PTPN13, FGFR3, FHIT, ATG7, LRP1B, MAPK1, DMD, KIAA1217, ...
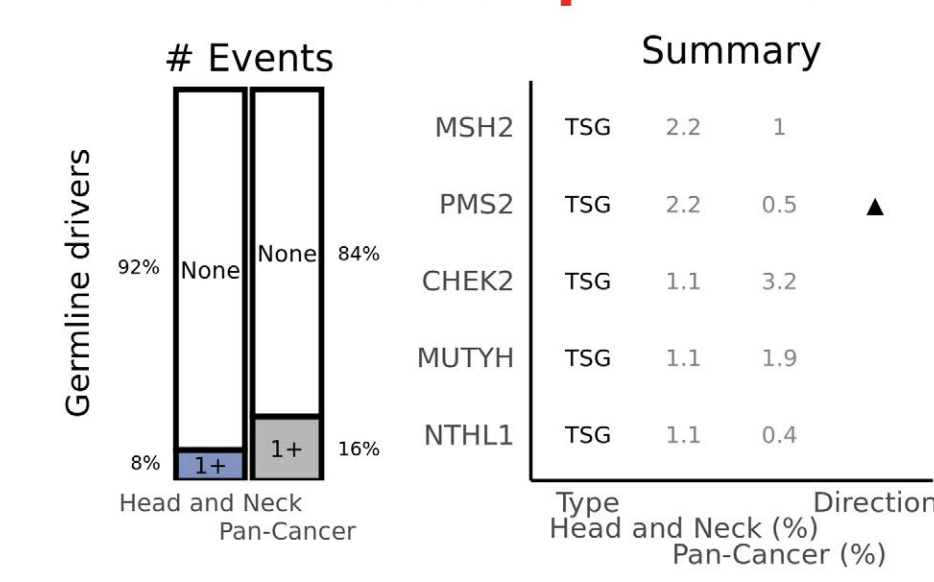
## Cancer Driver Landscape

### # Events

**Somatic drivers**: 30% / 44% / 69% / 54%
**Oncogenes**: 27% / 18% / 20% / 32% / 53% / 50%
**TSGs**: 10% / 61% / 29% / 33%

### Summary

| Gene | Type | Head and Neck (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 48 | 55 | ▼ |
| CDKN2A | TSG | 38 | 25 | ▲ |
| CCND1 | ONC | 13 | 5.6 | ▲ |
| PIK3CA | ONC | 13 | 13 | |
| FGF3 | ONC | 12 | 5.2 | ▲ |
| NOTCH1 | TSG | 12 | 13 | |
| MYB_NFIB | ONC | 10 | 0.2 | ▲ |
| CYLD | TSG | 7.9 | 1.9 | ▲ |
| DMD | TSG | 7.9 | 3.5 | ▲ |
| KMT2D | TSG | 7.9 | 2.9 | |
| TERT | ONC | 7.9 | 14 | ▼ |
| CSMD1 | TSG | 6.7 | 1.6 | ▲ |
| PTEN | TSG | 6.7 | 13 | ▼ |
| ATM | TSG | 5.6 | 2.9 | |
| ERBB2 | ONC | 5.6 | 5.7 | |
| FAT1 | TSG | 5.6 | 1.5 | ▲ |
| LRP1B | TSG | 5.6 | 2.1 | |
| NF1 | TSG | 5.6 | 5 | |
| B2M | TSG | 4.5 | 1.9 | |
| BAP1 | TSG | 4.5 | 2.7 | |
| DDX3X | TSG | 4.5 | 0.8 | ▲ |
| EGFR | ONC | 4.5 | 5.4 | |
| MDM2 | ONC | 4.5 | 3.3 | |
| PTPRD | TSG | 4.5 | 3 | |
| RB1 | TSG | 4.5 | 11 | ▼ |
| STK11 | TSG | 4.5 | 4.1 | |
| AJUBA | TSG | 3.4 | 0.3 | ▲ |
| ARID1A | TSG | 3.4 | 0.3 | ▲ |
| ATG7 | TSG | 3.4 | 0.4 | ▲ |

**Top cancer drivers** — 83 Patients

■ AMPLIFICATION ■ DELETION ■ MUTATION ■ FUSION

## Potentially Actionable Events

### # Events

**Actionable**: 29% / 18% / 18% / 26% / 53% / 56%
**Best treatment option**: 29% / 18% / 26% / 28% / 29% / 36% / 16%

### Summary

| Gene/Event | Head and Neck (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 38 | 24 | ▲ |
| PIK3CA | 13 | 13 | |
| CCND1 | 12 | 5.3 | ▲ |
| TMB High | 11 | 21 | ▼ |
| KMT2D | 7.9 | 2.9 | |
| PTEN | 6.7 | 13 | ▼ |
| ATM | 5.6 | 3.5 | |
| ERBB2 | 5.6 | 5.6 | |
| EGFR | 4.5 | 5.1 | |
| CD274 | 3.4 | 0.5 | ▲ |
| HRAS | 3.4 | 0.6 | ▲ |
| AKT1 | 2.2 | 1.4 | |
| BRAF | 2.2 | 5.9 | |
| CDK4 | 2.2 | 1.9 | |
| CTNNB1 | 2.2 | 2.7 | |
| FGFR3 | 2.2 | 1.2 | |
| HR deficiency | 2.2 | 5.8 | |
| BRAF - BRAF fusion | 1.1 | 0.1 | ▲ |
| BRCA1 | 1.1 | 1.3 | |
| BRCA2 | 1.1 | 2.4 | |
| CHEK2 | 1.1 | 3 | |
| EEA1 - RET fusion | 1.1 | | |
| FGFR1 | 1.1 | 3.8 | ▼ |
| Rest FDA | 2.2 | | |
| Rest Repurpose | 2.2 | | |
| Rest Experimental | 2.2 | | |
| Rest Other | 4.5 | | |

**Top potential actionable events** — 63 Patients

■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events

**Germline drivers**: 92% / 84% / 8% / 16%

### Summary

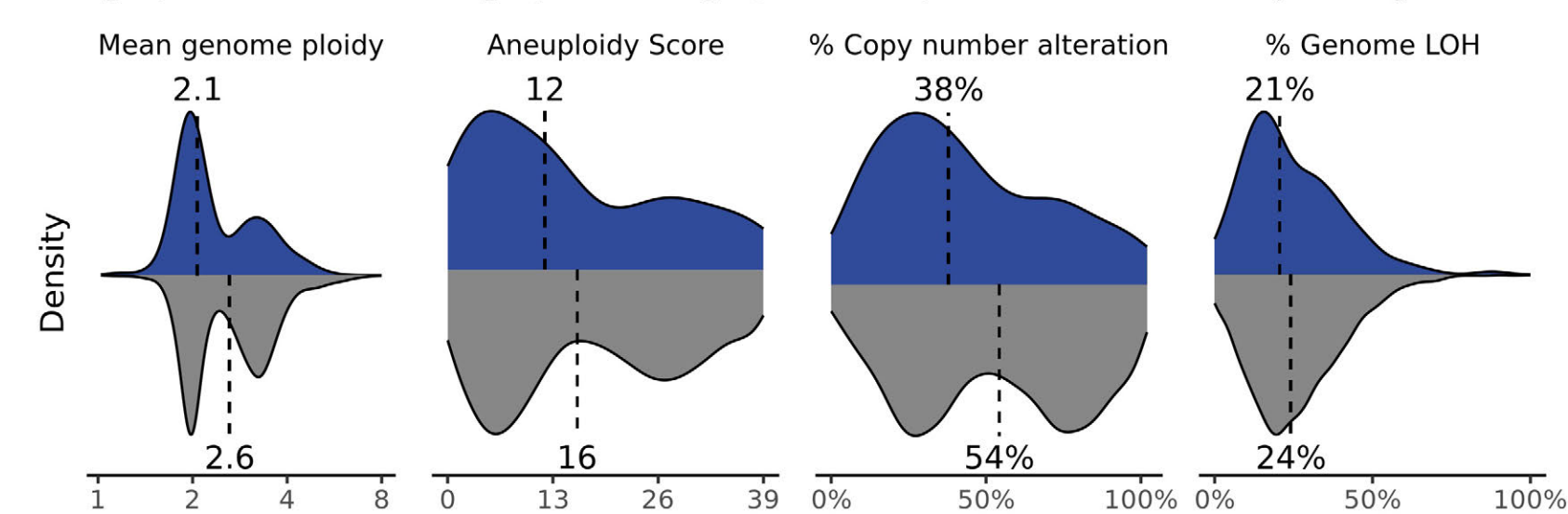| Gene | Type | Head and Neck (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MSH2 | TSG | 2.2 | 1 | |
| PMS2 | TSG | 2.2 | 0.5 | ▲ |
| CHEK2 | TSG | 1.1 | 3.2 | |
| MUTYH | TSG | 1.1 | 1.9 | |
| NTHL1 | TSG | 1.1 | 0.4 | |

**Top potential germline drivers** — 7 Patients

■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing ■ Other ■ Experimental/Other Guidelines ■ None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA | Repurposing | Other | Exp/Other | None |
|---|---|---|---|---|---|
| WGS | 14 | 26 | 12 | 15 | 22 |
| Comprehensive 521 gene panel | 13 | 22 | 13 | 15 | 26 |
| Targeted 50 gene panel | 5 | 19 | 3 | 21 | 41 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | Total |
|---|---|---|---|---|
| WGS | 0.47 | 0.31 | 0.79 | 1.8 |
| Comprehensive 521 gene panel | 0.37 | 0.24 | 0.56 | 1.3 |
| Targeted 50 gene panel | 0.26 | 0.4 | | 0.8 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

| FDA Approved | | Drug Repurposing | |
|---|---|---|---|
| Fusion | 1 | Partial CN Loss | 5 |
| | | Fusion | 2 |
| | | HRD | 2 |

| Experimental/Other Guidelines | | Other | |
|---|---|---|---|
| Partial CN Loss | 5 | Partial CN Loss | 14 |
| Fusion | 1 | HMZ Disruption | 3 |
| Full CN Gain | 1 | Full CN Loss | 3 |

### Top missed events by Targeted Panel vs WGS

| FDA Approved | | Drug Repurposing | |
|---|---|---|---|
| TMB High | 10 | Small Variant | 10 |
| Fusion | 1 | Partial CN Loss | 5 |
| | | Fusion | 2 |
| | | HRD | 2 |

| Experimental/Other Guidelines | | Other | |
|---|---|---|---|
| Full CN Gain | 13 | Partial CN Loss | 14 |
| Partial CN Loss | 5 | Small Variant | 13 |
| Small Variant | 2 | HMZ Disruption | 3 |
| Full CN Loss | 2 | Full CN Loss | 3 |
| Fusion | 1 | Splice Site | 1 |

Number of Missed Events

# The Genomic And Actionability Landscape Of Renal Clear Cell Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 150 |
| RNASeq | 95 |
| Age, Sex | 118 |
| Biopsy site | 113 |
| Pretreatment | 118 |
| Treatment | 117 |
| Response | 89 |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 3 | 2 (67%) |
| Multiple | 6 | 4 (67%) |
| Targeted | 63 | 12 (19%) |
| Hormonal | 0 | |
| Immuno | 19 | 3 (16%) |
| Radio | 18 | 5 (28%) |
| Other | 0 | |
| None or NA | 0 | 0 |

## Processes Underlying Mutations

- DNA damage repair: 15%
- Chemical exposure: 10%
- Ageing: 8%
- Tobacco: 5%
- APOBEC: 4%
- UV light: 1%
- Unknown: 57%

## Tumor Characteristics

Kidney / Pan-Cancer

| | Kidney | Pan-Cancer |
|---|---|---|
| TMB High | 1% | 21% |
| MSI High | 1% | 2% |
| WGD | 35% | 56% |
| Diploid Proportion | 48% | 34% |
| GIE HLA LOH | 21% | 19% |
| GIE Overall | 25% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 1% | 6% |

**Kidney 150 Patients**
**Pan-Cancer 6790 Patients**

Kidney

## Mutational Landscape

**Tumor purity** — 42% / 55%
**Clonal mutation fraction** — 97% / 95%
**Tumor mutational burden** — 2.7 / 4.2, High 1% / 21%

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Kidney | 6,852 | 854 | 59 | 90 |

**Telomere Length** — 0.73 / 0.82
**VDJ CDR3 Sequences** — 8 / 6
**Microsatellite instability** — 0.07 / 0.15, Instable 1% / 2%

**Mean genome ploidy** — 2.1 / 2.6
**Aneuploidy Score** — 12 / 16
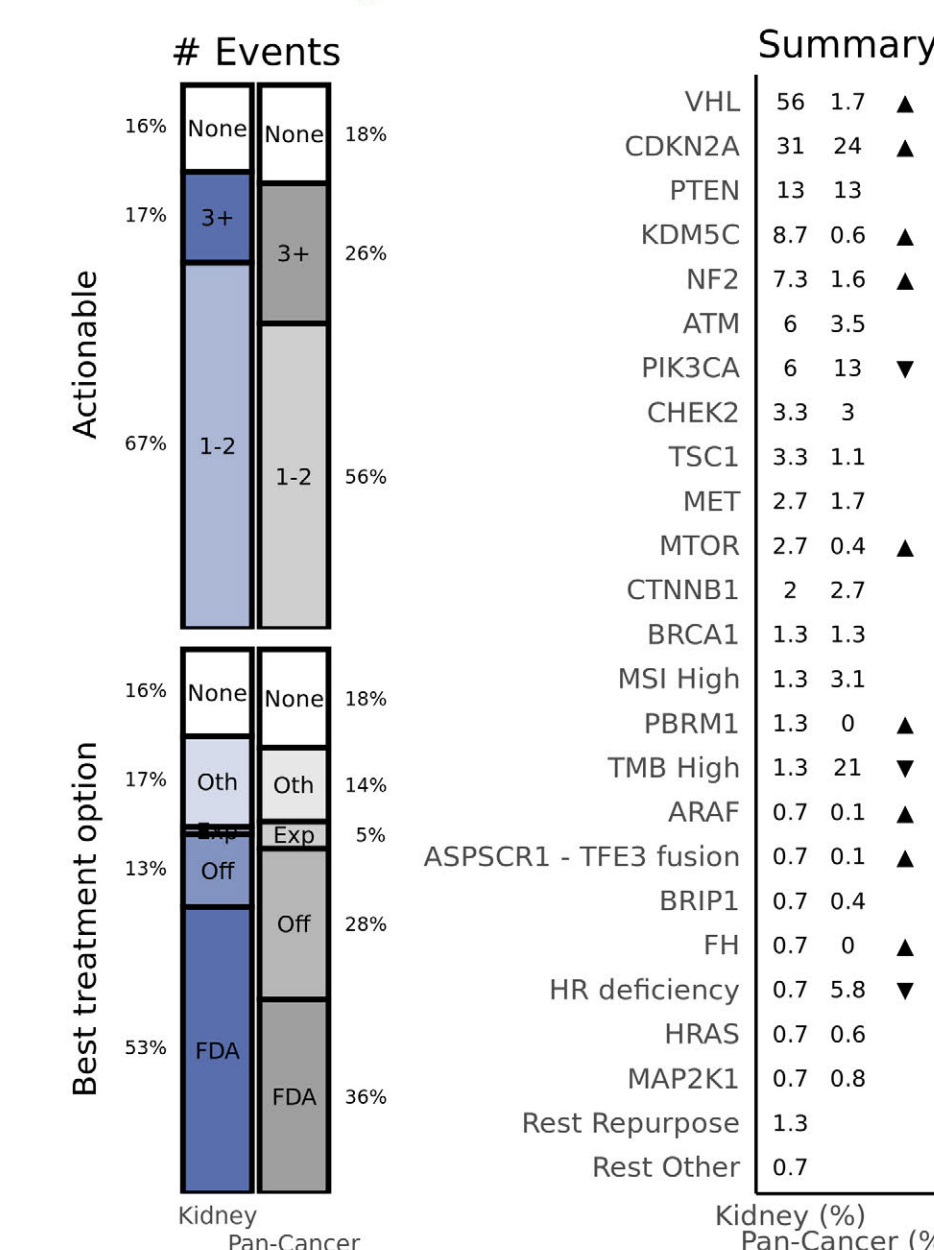**% Copy number alteration** — 38% / 54%
**% Genome LOH** — 21% / 24%
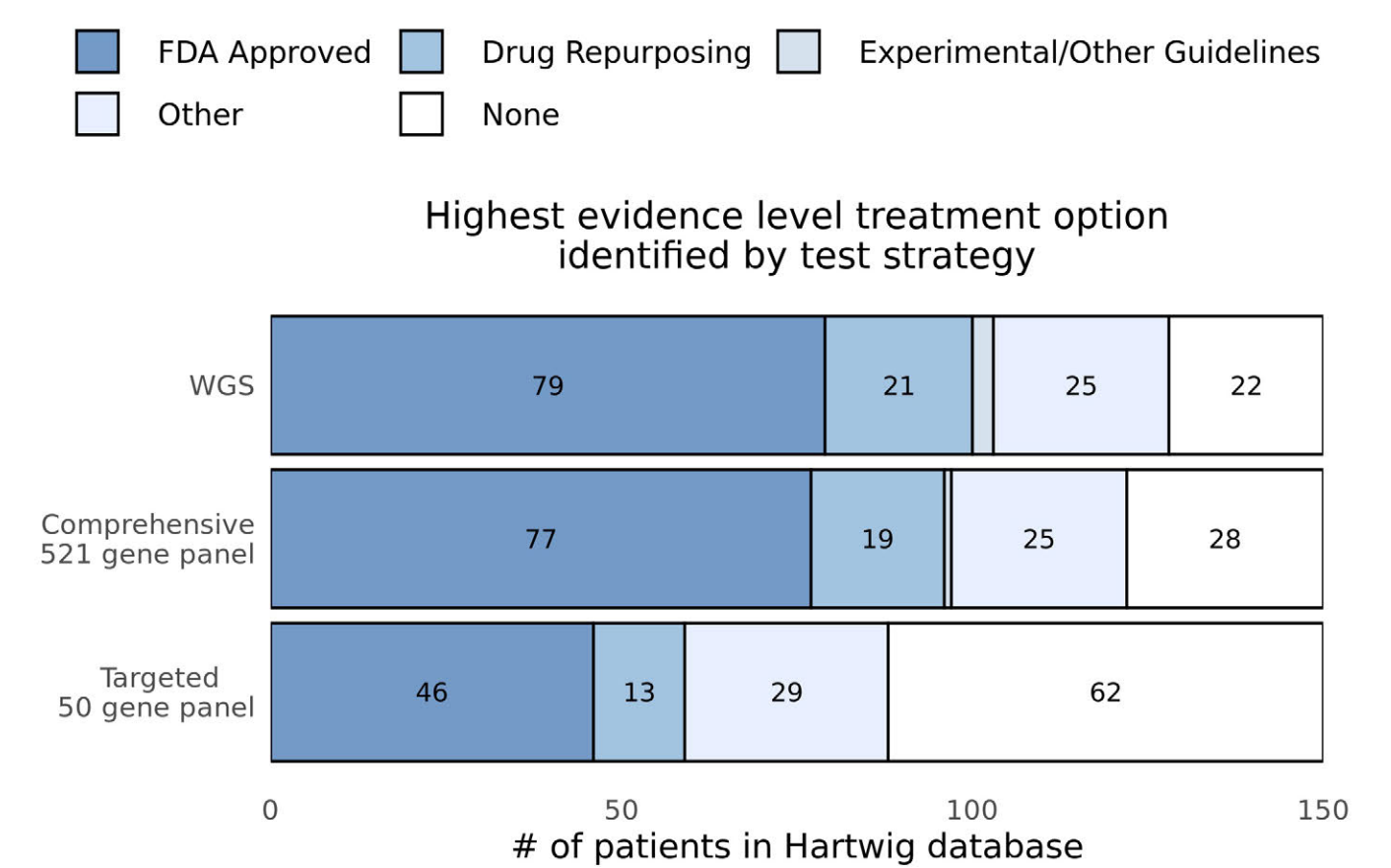
## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

| Gene | Type | Kidney (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| VHL | TSG | 56 | 1.6 | ▲ |
| PBRM1 | TSG | 43 | 3.2 | ▲ |
| CDKN2A | TSG | 31 | 25 | |
| SETD2 | TSG | 25 | 2.1 | ▲ |
| TP53 | TSG | 18 | 55 | ▼ |
| TERT | ONC | 16 | 13 | |
| PTEN | ONC | 13 | 14 | |
| BAP1 | TSG | 12 | 2.7 | ▲ |
| PTPRD | TSG | 11 | 5.6 | |
| ARID1A | TSG | 10 | 6 | |
| KDM5C | TSG | 8.7 | 0.5 | ▲ |
| NF2 | TSG | 7.3 | 1.7 | ▲ |
| PIK3CA | ONC | 6 | 13 | ▼ |
| ATM | TSG | 4.7 | 2.9 | |
| NEGR1 | TSG | 4 | 0.3 | ▲ |
| B2M | TSG | 3.3 | 1.9 | |
| KEAP1 | TSG | 3.3 | 2.2 | |
| LRP1B | TSG | 3.3 | 2.1 | |
| TSC1 | TSG | 3.3 | 1.1 | ▲ |
| AR | ONC | 2.7 | 5.6 | |
| CYLD | TSG | 2.7 | 1.3 | |
| MET | ONC | 2.7 | 0.8 | ▲ |
| MGA | TSG | 2.7 | 1.5 | |
| MTOR | ONC | 2.7 | 0.5 | ▲ |
| NIPBL | TSG | 2.7 | 0.6 | |
| SAV1 | TSG | 2.7 | 0.3 | ▲ |
| TET2 | TSG | 2.7 | 2.5 | |
| ATG7 | TSG | 2 | 0.4 | ▲ |
| CTNNB1 | ONC | 2 | 2.9 | |

Kidney / Pan-Cancer

**Top cancer drivers** — 137 Patients

Legend: AMPLIFICATION / DELETION / MUTATION

## Potentially Actionable Events

### # Events / Summary

| Gene | Kidney (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| VHL | 56 | 1.7 | ▲ |
| CDKN2A | 31 | 24 | |
| PTEN | 13 | 13 | |
| KDM5C | 8.7 | 0.6 | ▲ |
| NF2 | 7.3 | 1.6 | ▲ |
| ATM | 6 | 3.5 | |
| PIK3CA | 6 | 13 | ▼ |
| CHEK2 | 3.3 | 3 | |
| TSC1 | 3.3 | 1.1 | |
| MET | 2.7 | 1.7 | |
| MTOR | 2.7 | 0.4 | ▲ |
| CTNNB1 | 2 | 2.7 | |
| BRCA1 | 1.3 | 1.3 | |
| MSI High | 1.3 | 3.1 | |
| PBRM1 | 1.3 | 0 | ▲ |
| TMB High | 1.3 | 21 | ▼ |
| ARAF | 0.7 | 0.1 | ▲ |
| ASPSCR1 - TFE3 fusion | 0.7 | 0.1 | |
| BRIP1 | 0.7 | 0.4 | |
| FH | 0.7 | 0 | ▲ |
| HR deficiency | 0.7 | 5.8 | ▼ |
| HRAS | 0.7 | 0.6 | |
| MAP2K1 | 0.7 | 0.8 | |
| Rest Repurpose | 1.3 | | |
| Rest Other | 0.7 | | |

Kidney / Pan-Cancer

**Top potential actionable events** — 126 Patients

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

### # Events / Summary

| Gene | Type | Kidney (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 2.7 | 3.2 | |
| BRCA1 | TSG | 2 | 1.1 | |
| MSH2 | TSG | 2 | 1 | |
| MUTYH | TSG | 2 | 1.9 | |
| ATM | TSG | 1.3 | 1 | |
| EPCAM | TSG | 1.3 | 0.1 | ▲ |
| FH | TSG | 1.3 | 0.1 | ▲ |
| BRIP1 | TSG | 0.7 | 0.2 | ▲ |
| CDH1 | TSG | 0.7 | 0.1 | ▲ |

Kidney / Pan-Cancer

**Top potential germline drivers** — 19 Patients

Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Other / None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Experimental/Other | Other |
|---|---|---|---|---|
| WGS | 79 | 21 | 25 | 22 |
| Comprehensive 521 gene panel | 77 | 19 | 25 | 28 |
| Targeted 50 gene panel | 46 | 13 | 29 | 62 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.57 | 0.3 | | 0.64 | 1.6 |
| Comprehensive 521 gene panel | 0.55 | 0.27 | 0.48 | | 1.4 |
| Targeted 50 gene panel | 0.33 | 0.33 | | | 0.8 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved
- Partial CN Loss — 2

Drug Repurposing
- Partial CN Loss — 1
- HRD — 1
- Partial CN Gain — 1

Experimental/Other Guidelines
- Partial CN Loss — 5

Other
- Partial CN Loss — 17
- HMZ Disruption — 3
- Full CN Loss — 3
- Fusion — 1

### Top missed events by Targeted Panel vs WGS

FDA Approved
- Small Variant — 24
- Splice Site — 7
- Partial CN Loss — 2
- TMB High — 2

Drug Repurposing
- Small Variant — 18
- Splice Site — 4
- Partial CN Loss — 2
- HRD — 1
- Partial CN Gain — 1

Experimental/Other Guidelines
- Small Variant — 10
- Partial CN Loss — 5
- Splice Site — 2
- Full CN Gain — 1
- Full CN Loss — 1

Other
- Small Variant — 18
- Partial CN Loss — 17
- Splice Site — 4
- HMZ Disruption — 3
- Full CN Loss — 3

Number of Missed Events

## Panel annotations and abbreviations

Made with bioRender

# The Genomic And Actionability Landscape Of Hepatocellular Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 54 |
| RNASeq | 42 |
| Age, Sex | 50 |
| Biopsy site | 50 |
| Pretreatment | 50 |
| Treatment | 4 |
| Response | 29 |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | Treatment | Responders |
|---|---|---|
| Chemo | 0 | 0 |
| Multiple | 0 | 0 |
| Targeted | 28 | 3 (11%) |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 0 | 0 |
| Other | 1 | 0 |
| None or NA | 0 | 0 |

## Processes Underlying Mutations

- Chemical exposure: 15%
- Tobacco: 14%
- Ageing: 12%
- DNA damage repair: 10%
- APOBEC: 2%
- UV light: 1%
- Unknown: 46%

## Tumor Characteristics

Liver (dark) / Pan-Cancer (grey)

| | Liver | Pan-Cancer |
|---|---|---|
| TMB High | 0% | 21% |
| MSI High | 0% | 2% |
| WGD | 43% | 56% |
| Diploid Proportion | 43% | 34% |
| GIE HLA LOH | 2% | 19% |
| GIE Overall | 11% | 26% |
| Viral Insertions | 11% | 3% |
| HRD | 4% | 6% |

**Liver: 54 Patients**
**Pan-Cancer: 6790 Patients**

## Mutational Landscape

### Tumor purity
52% (Liver), 55% (Pan-Cancer)

### Clonal mutation fraction
94% (Liver), 95% (Pan-Cancer)

### Tumor mutational burden
4.2 — High 0% (Liver), 21% (Pan-Cancer)
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Liver | 10,957 | 936 | 102 | 148 |
| Pan-Cancer | 10,846 | 983 | 183 | 92 |

Number of variants / Quantile

### Telomere Length
0.78 (Liver) / 0.82 (Pan-Cancer)
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
8 (Liver) / 6 (Pan-Cancer)
Log2 (CDR3 + 1)

### Microsatellite instability
0.13 — Instable 0% (Liver), 0.15 — 2% (Pan-Cancer)
MS indels per megabase

### Mean genome ploidy
2.2 / 2.6

### Aneuploidy Score
10 / 16

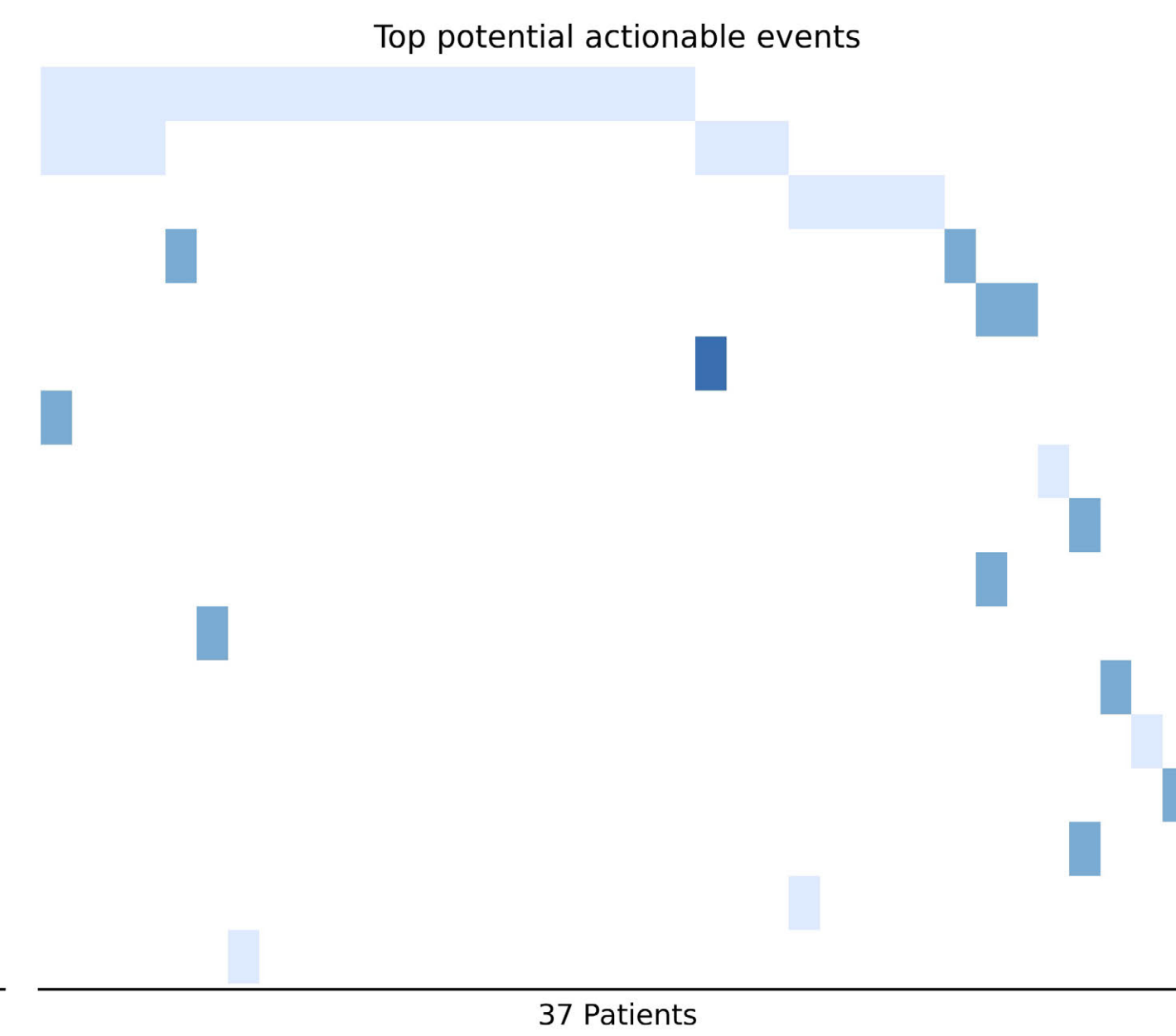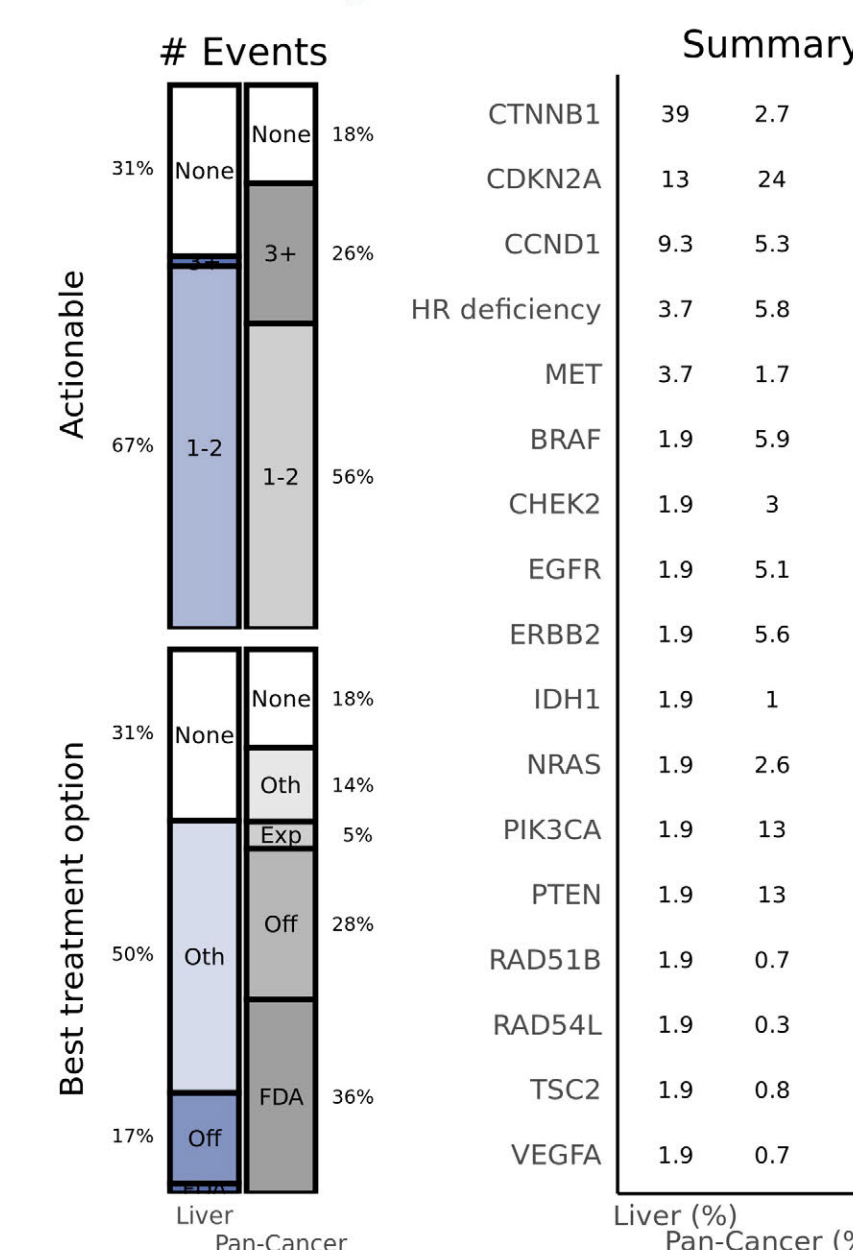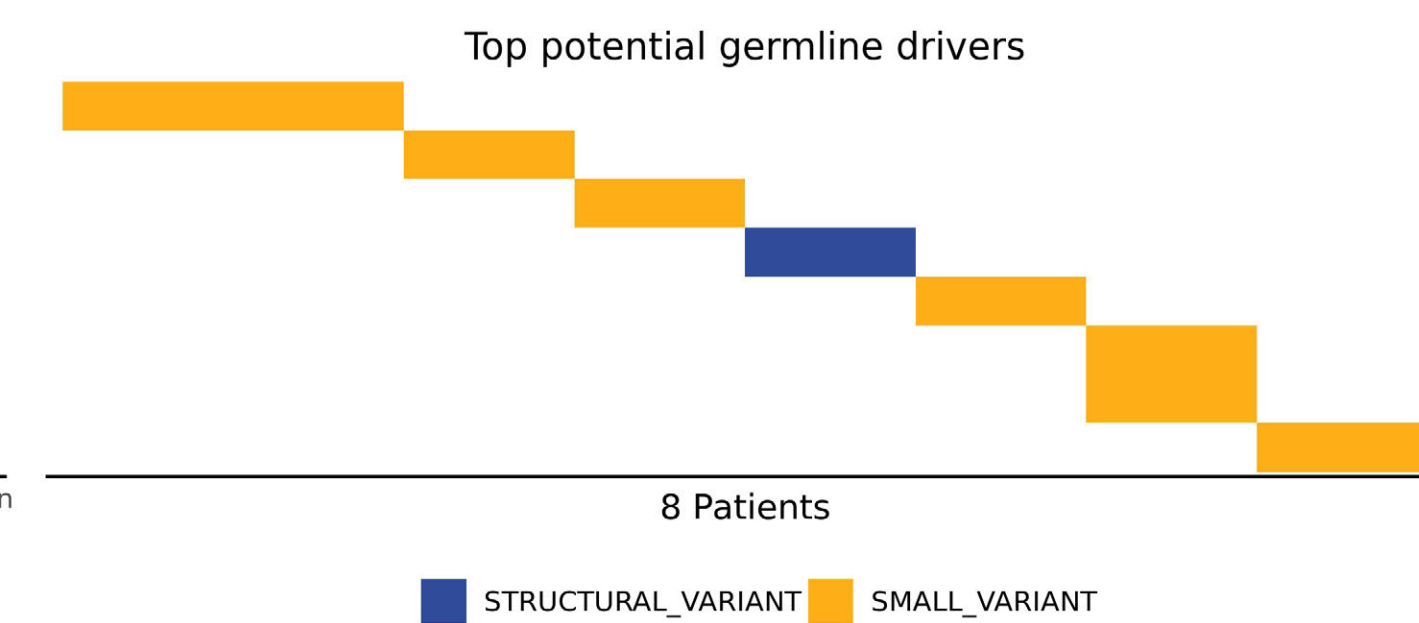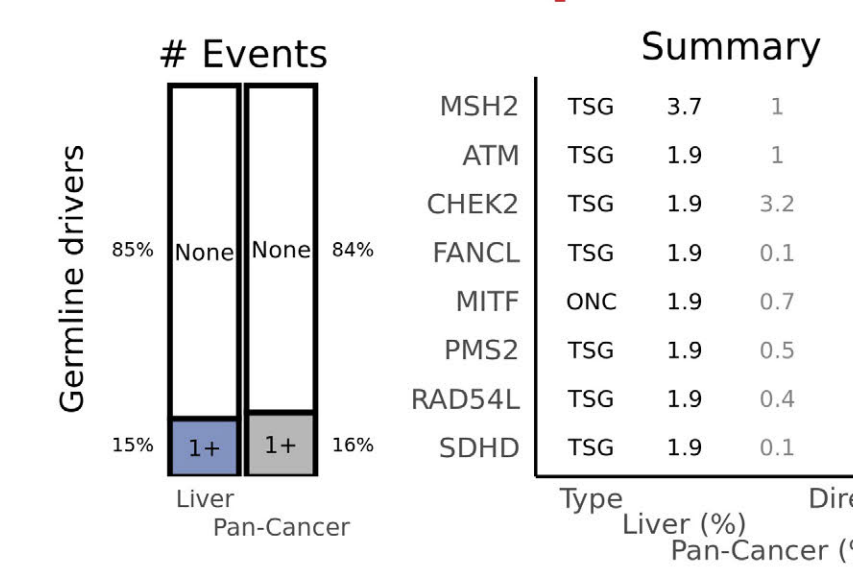### % Copy number alteration
36% / 54%

### % Genome LOH
16% / 24%

## Copy Number Alteration Profile

## Cancer Driver Landscape

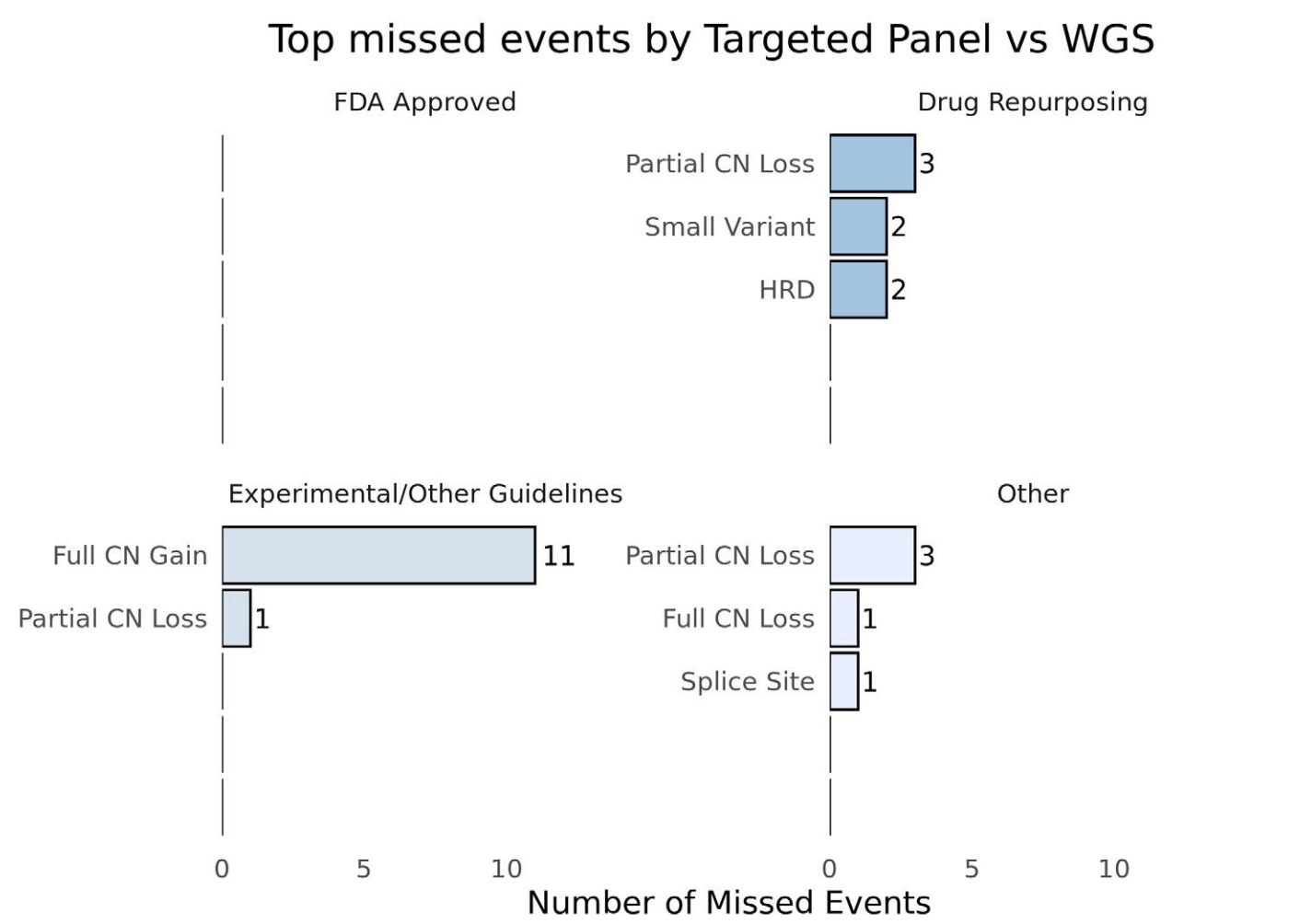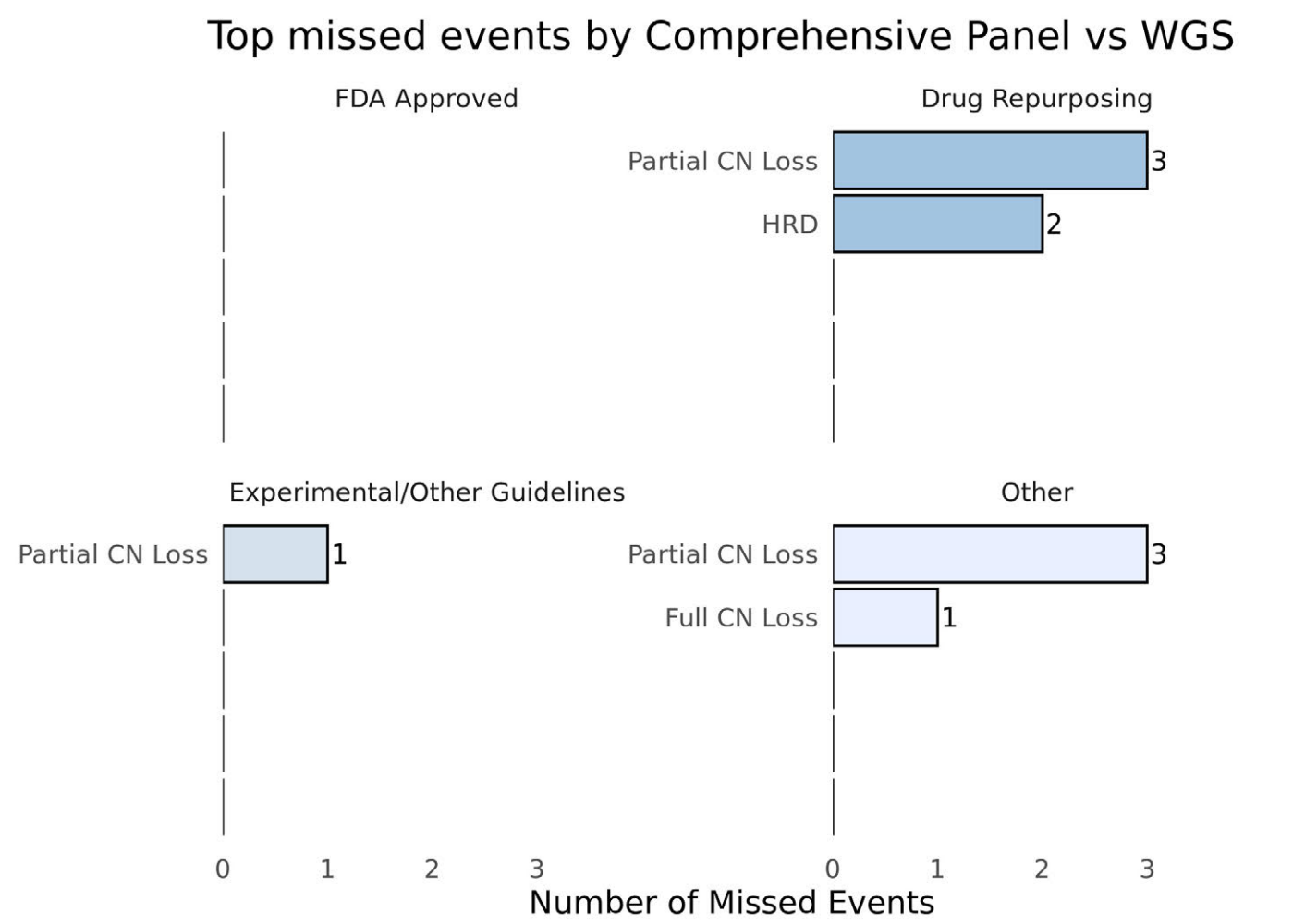### # Events

Somatic drivers: 20% 6+ / 44% 6+; 80% 1-5 / 54% 1-5
Oncogenes: 13% None / 6% None; 20% 3+ / 32% 3+; 67% 1-2 / 50% 1-2
TSGs: 7% None / 6% None; 28% 3+ / 61% 3+; 65% 1-2 / 33% 1-2

### Summary

| Gene | Type | Liver (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TERT | ONC | 61 | 13 | |
| TP53 | TSG | 43 | 55 | ▼ |
| CTNNB1 | ONC | 39 | 2.9 | ▲ |
| CDKN2A | TSG | 13 | 25 | ▼ |
| PABPC1 | ONC | 11 | 2.3 | ▲ |
| CCND1 | ONC | 9.3 | 5.6 | |
| MYC | ONC | 9.3 | 5.7 | |
| NCOA2 | ONC | 9.3 | 1.6 | ▲ |
| TG | ONC | 9.3 | 2.3 | ▲ |
| ZBTB10 | ONC | 9.3 | 2.1 | ▲ |
| ARID2 | TSG | 7.4 | 1.8 | ▲ |
| AXIN1 | TSG | 7.4 | 0.6 | ▲ |
| PREX2 | ONC | 7.4 | 2.3 | ▲ |
| RAD21 | ONC | 7.4 | 2.6 | |
| ARID1A | TSG | 5.6 | 6 | |
| KMT2B | TSG | 5.6 | 1 | ▲ |
| PBRM1 | TSG | 5.6 | 3.2 | |
| RB1 | TSG | 5.6 | 11 | ▼ |
| RPS6KA3 | TSG | 5.6 | 0.1 | ▲ |
| AMER1 | TSG | 3.7 | 1.4 | |
| CREBBP | TSG | 3.7 | 1.9 | |
| CSMD1 | TSG | 3.7 | 0.8 | |
| DDX3X | TSG | 3.7 | 0.8 | ▲ |
| DLG2 | TSG | 3.7 | 0.1 | ▲ |
| DNAJB1_PRKACA | ONC | 3.7 | 0 | ▲ |
| FGF3 | ONC | 3.7 | 5.2 | |
| JAK1 | TSG | 3.7 | 1.1 | ▲ |
| KANSL1 | TSG | 3.7 | 0.3 | ▲ |
| MET | ONC | 3.7 | 1.8 | |

### Top cancer drivers
53 Patients

Legend: AMPLIFICATION / DELETION / MUTATION / FUSION

## Potentially Actionable Events

### # Events

Actionable: 31% None / 18% None; 26% 3+; 67% 1-2 / 56% 1-2
Best treatment option: 31% None / 14% Oth; 5% Exp; 50% Oth / 28% Off; 17% Off / 36% FDA

### Summary

| Gene | Liver (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CTNNB1 | 39 | 2.7 | |
| CDKN2A | 13 | 24 | ▼ |
| CCND1 | 9.3 | 5.3 | |
| HR deficiency | 3.7 | 5.8 | |
| MET | 3.7 | 1.7 | |
| BRAF | 1.9 | 5.9 | ▼ |
| CHEK2 | 1.9 | 3 | |
| EGFR | 1.9 | 5.1 | |
| ERBB2 | 1.9 | 5.6 | ▼ |
| IDH1 | 1.9 | 1 | |
| NRAS | 1.9 | 2.6 | |
| PIK3CA | 1.9 | 13 | ▼ |
| PTEN | 1.9 | 13 | ▼ |
| RAD51B | 1.9 | 0.7 | |
| RAD54L | 1.9 | 0.3 | ▲ |
| TSC2 | 1.9 | 0.8 | |
| VEGFA | 1.9 | 0.7 | |

### Top potential actionable events
37 Patients

Legend: FDA Approved / Drug Repurposing / Other

## Germline Predisposition

### # Events
Germline drivers: 85% None / 84% None; 15% 1+ / 16% 1+

### Summary

| Gene | Type | Liver (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MSH2 | TSG | 3.7 | 1 | ▲ |
| ATM | TSG | 1.9 | 1 | |
| CHEK2 | TSG | 1.9 | 3.2 | |
| FANCL | TSG | 1.9 | 0.1 | ▲ |
| MITF | ONC | 1.9 | 0.7 | |
| PMS2 | TSG | 1.9 | 0.1 | ▲ |
| RAD54L | TSG | 1.9 | 0.4 | ▲ |
| SDHD | TSG | 1.9 | 0.1 | ▲ |

### Top potential germline drivers
8 Patients

Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Other / Experimental/Other Guidelines / None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Exp/Other | None |
|---|---|---|---|---|
| WGS | 11 | 13 | 16 | 13 |
| Comprehensive 521 gene panel | 6 | 13 | 19 | 15 |
| Targeted 50 gene panel | 5 | 2 | 21 | 25 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | Total |
|---|---|---|---|---|
| WGS | 0.24 | 0.26 | 0.56 | 1.1 |
| Comprehensive 521 gene panel | 0.24 | 0.48 | | 0.9 |
| Targeted 50 gene panel | 0.46 | | | 0.6 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved — (none)
Drug Repurposing: Partial CN Loss 3, HRD 2
Experimental/Other Guidelines: Partial CN Loss 1
Other: Partial CN Loss 3, Full CN Loss 1

### Top missed events by Targeted Panel vs WGS

FDA Approved — (none)
Drug Repurposing: Partial CN Loss 3, Small Variant 2, HRD 2
Experimental/Other Guidelines: Full CN Gain 11, Partial CN Loss 1
Other: Partial CN Loss 3, Full CN Loss 1, Splice Site 1

Number of Missed Events
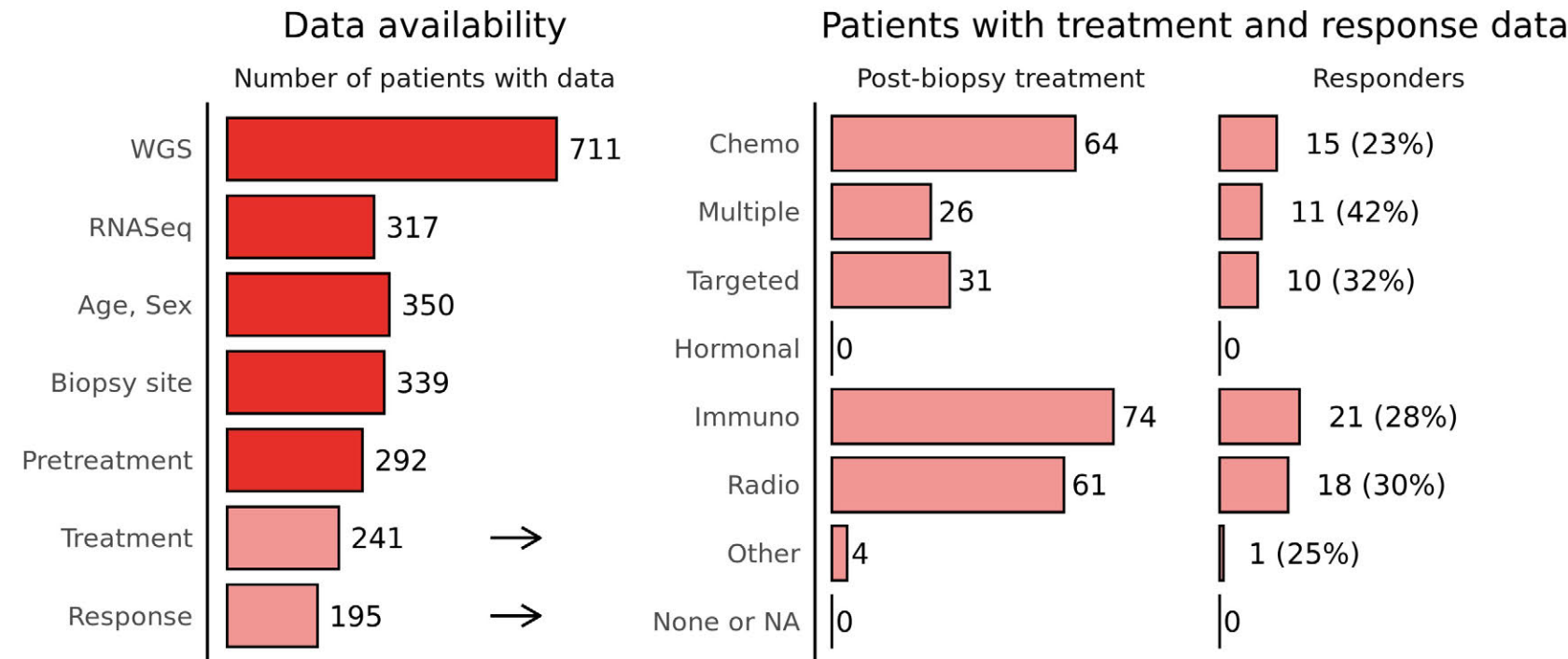
## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6x sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3x sample ploidy; dark red), moderate amplification (>2x sample ploidy; red) and low level amplification (>1.4 x sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: LIHC
DOIDs included: 684
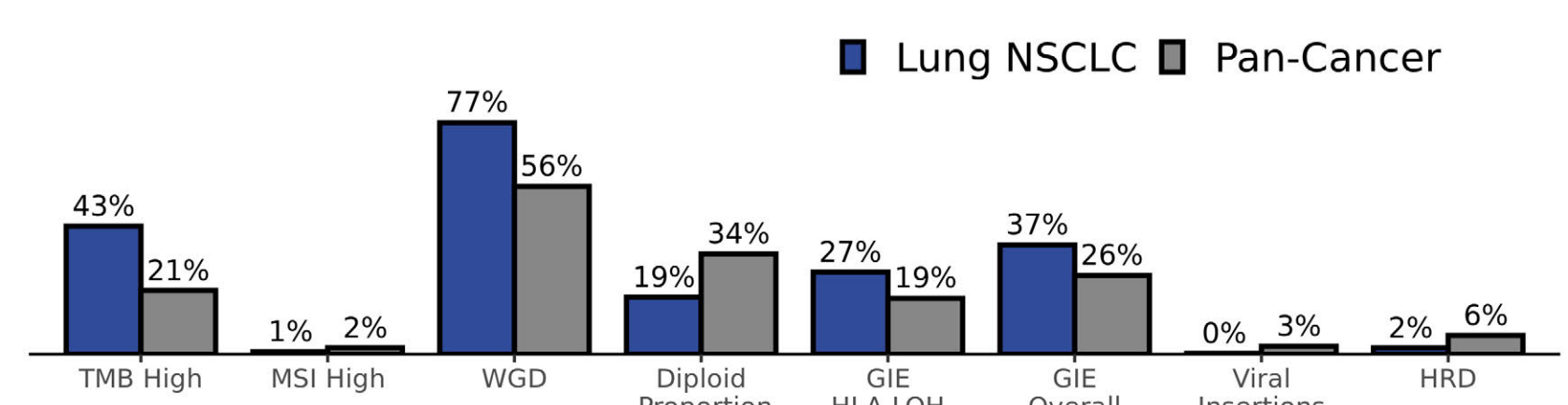Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
- Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
- Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
- Copy number: Events for panel genes with min copy number < 0.5 or max copy number > 6 assumed covered.
- Other events: Fusions, HMZ (homozygous) Distruptions, Viral inserts, HLA type assumed not captured by panels.
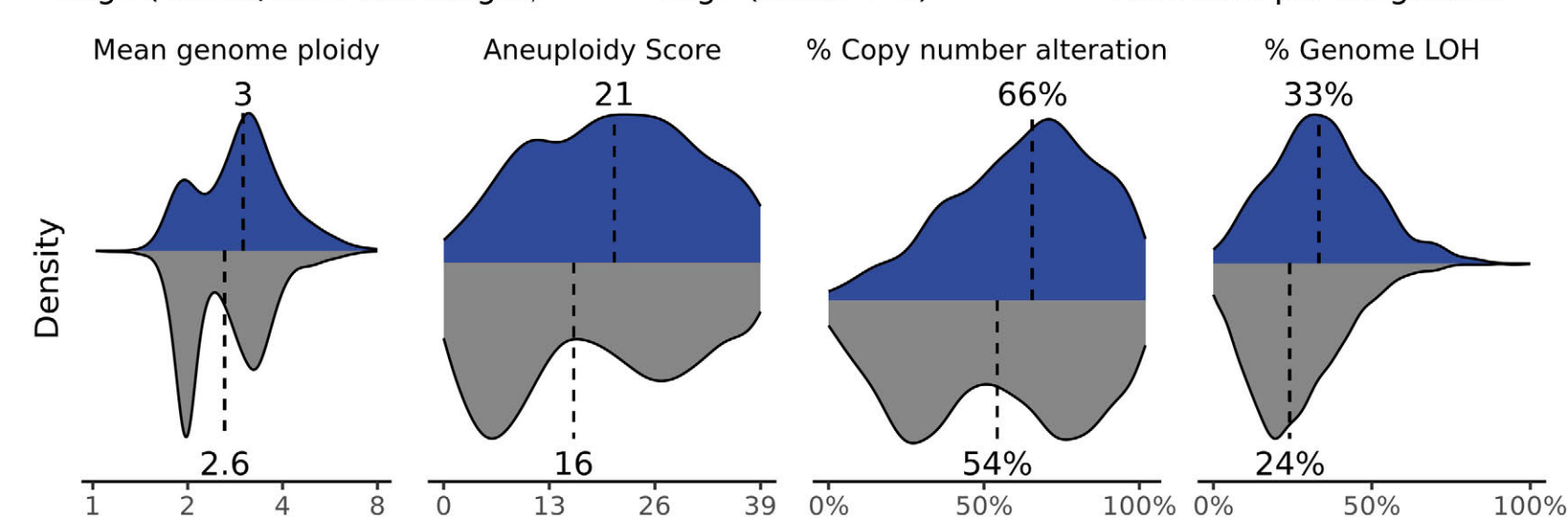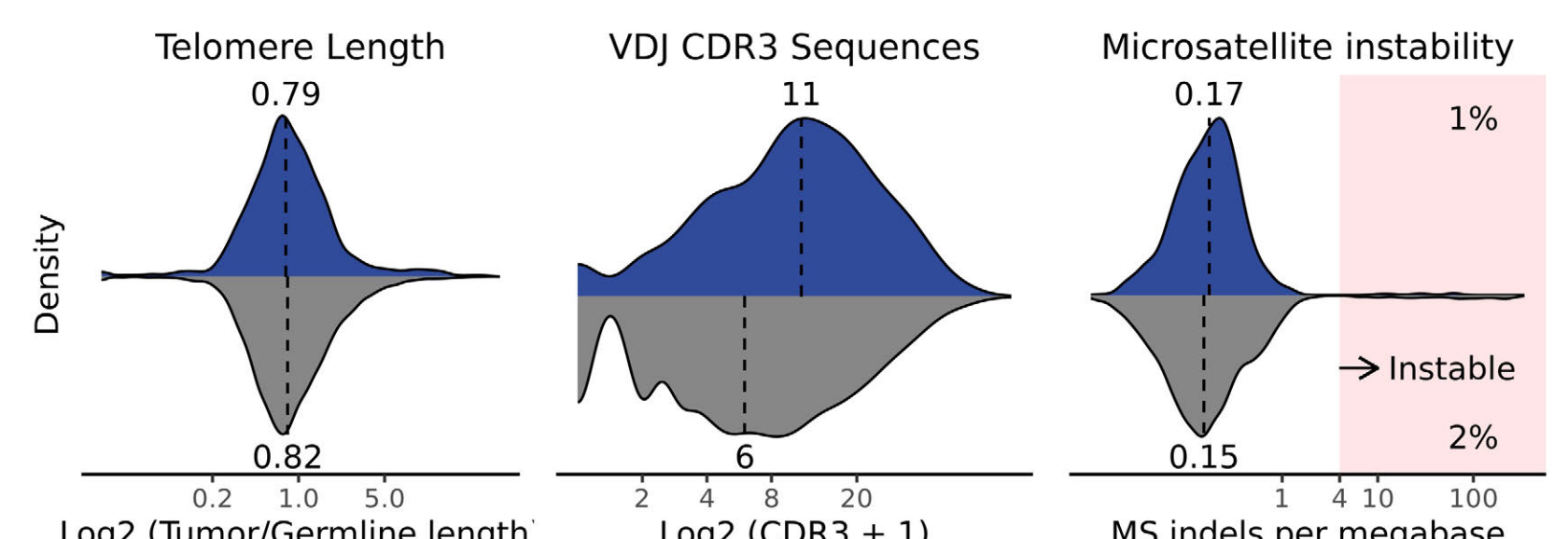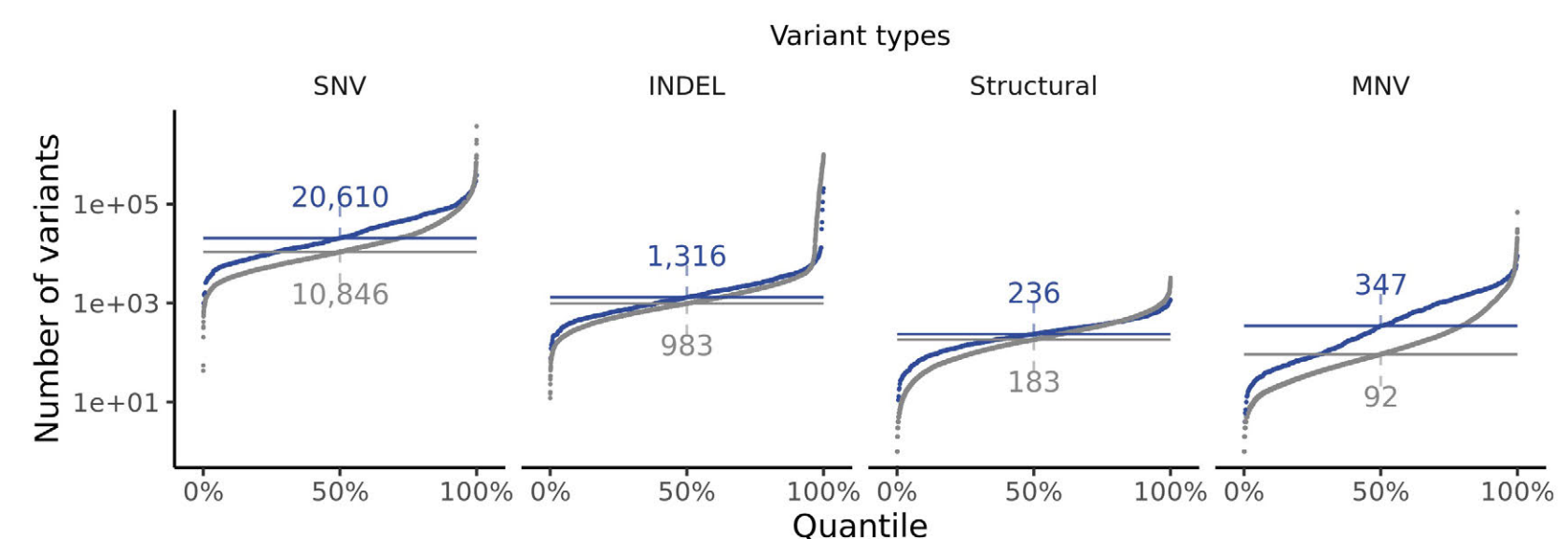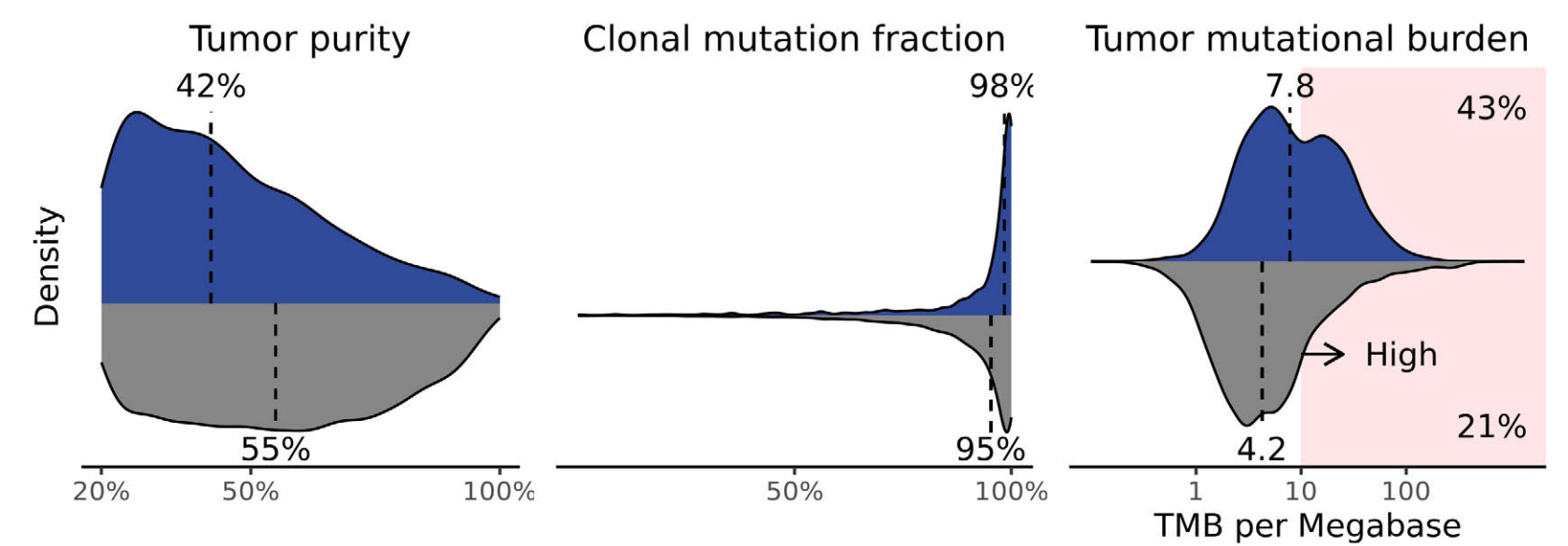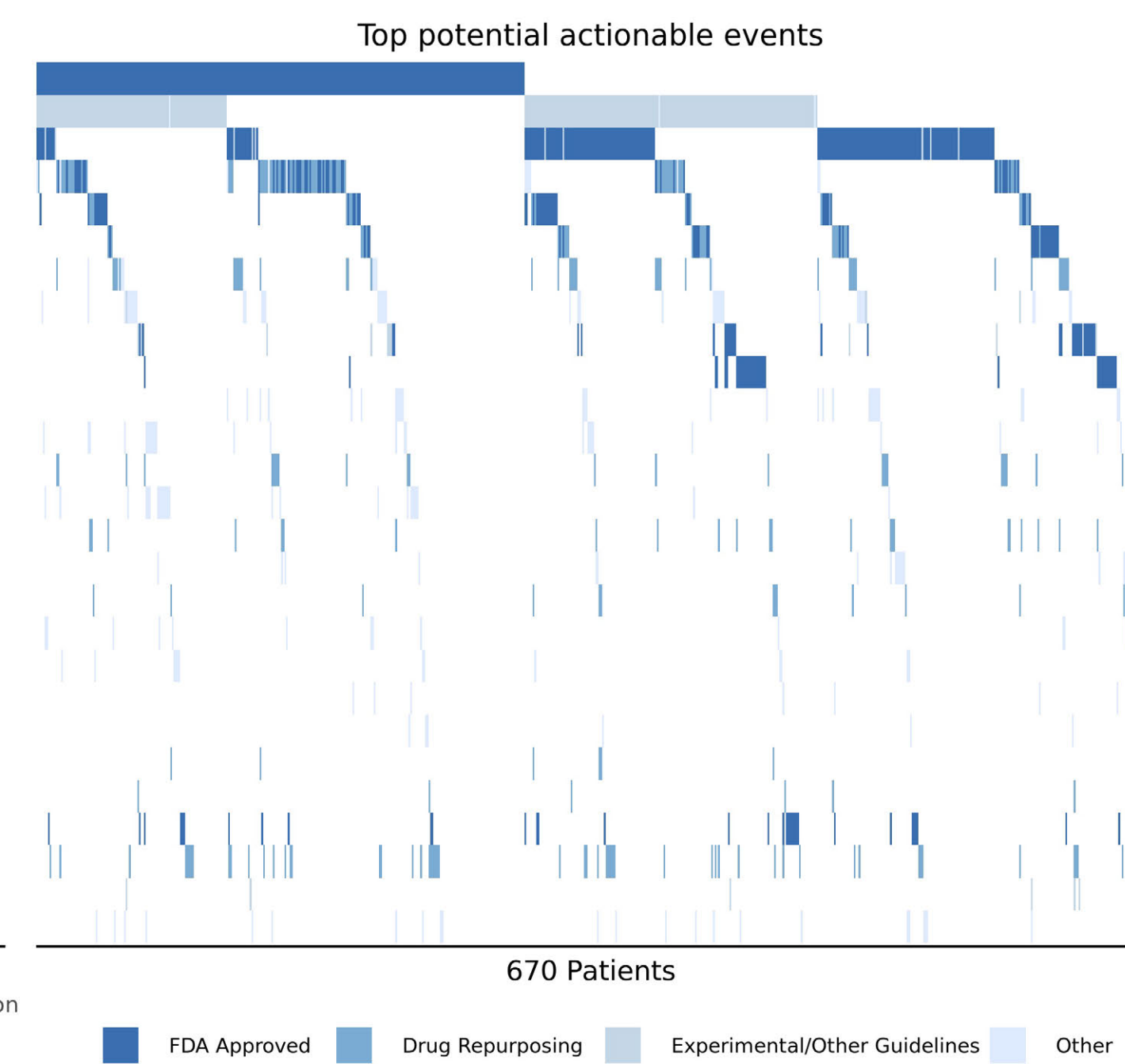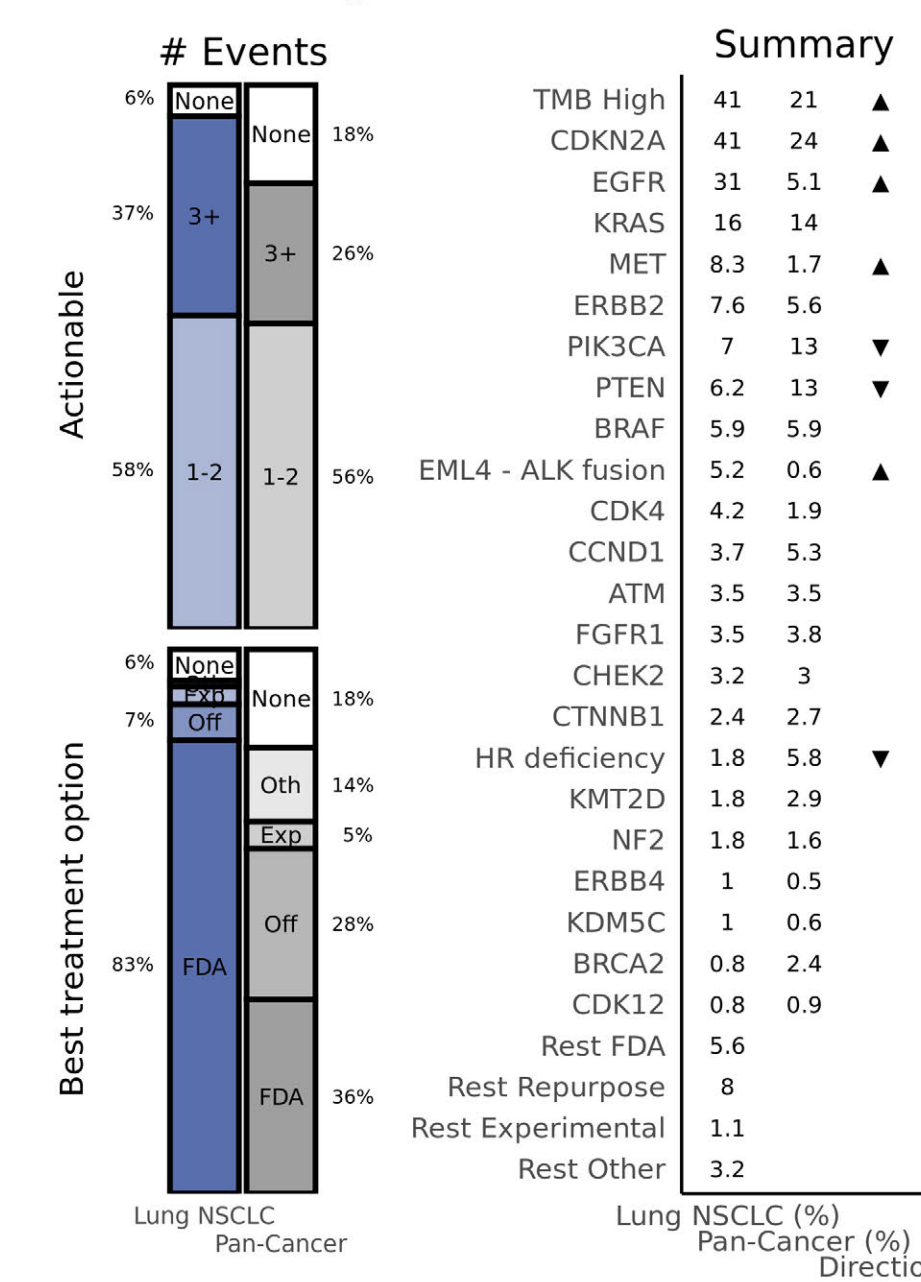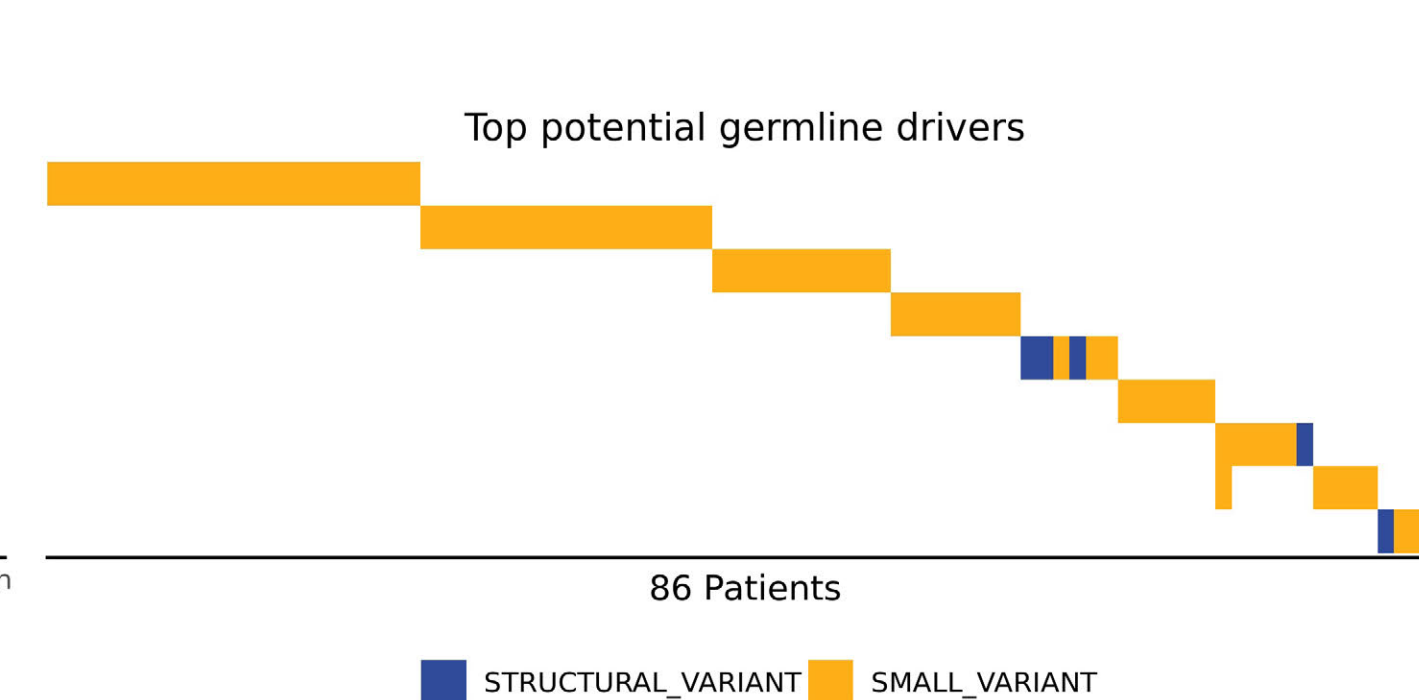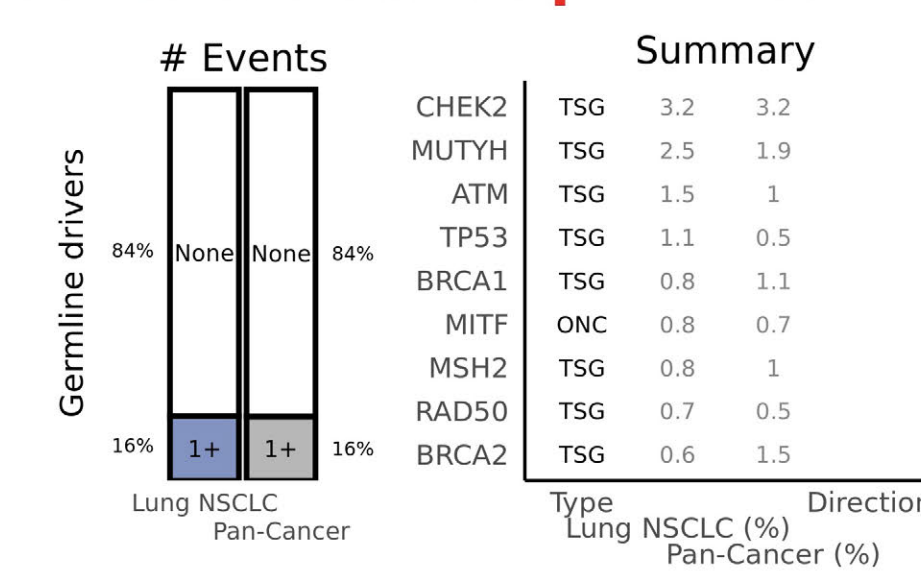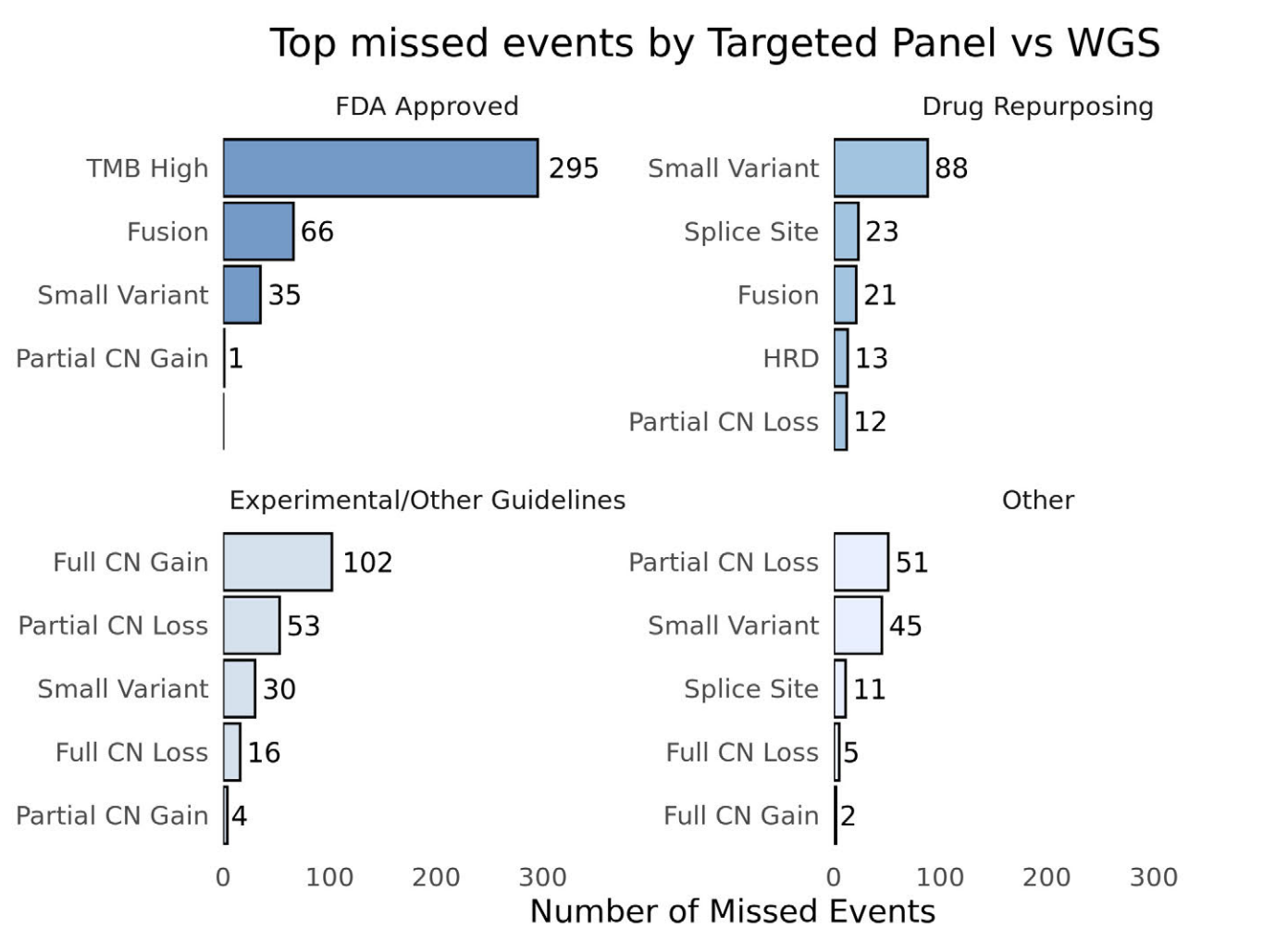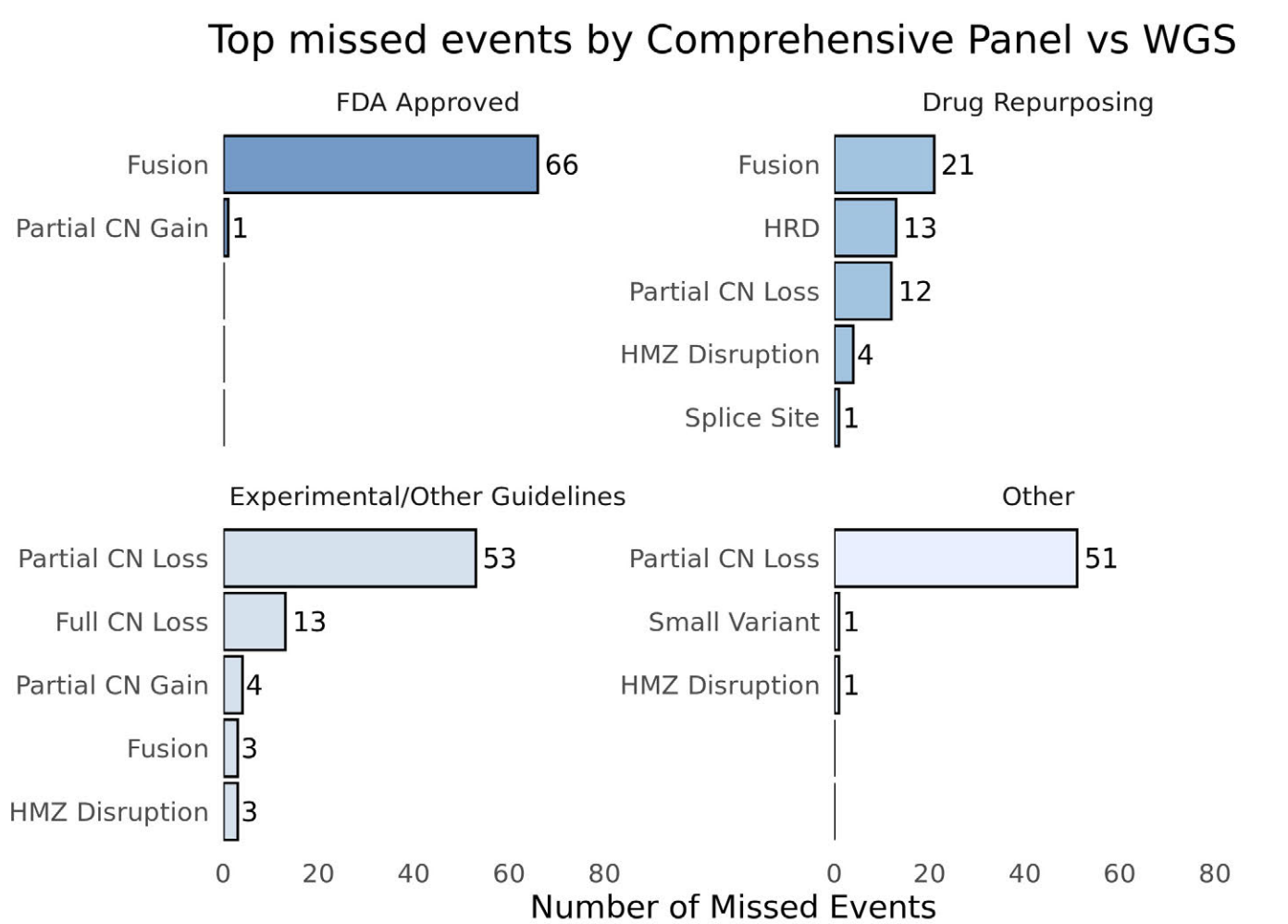** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Lung Non-Small Cell Carcinoma

## Cohort Metadata

### Data availability
Number of patients with data

| | |
|---|---|
| WGS | 711 |
| RNASeq | 317 |
| Age, Sex | 350 |
| Biopsy site | 339 |
| Pretreatment | 292 |
| Treatment | 241 → |
| Response | 195 → |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | | |
|---|---|---|
| Chemo | 64 | 15 (23%) |
| Multiple | 26 | 11 (42%) |
| Targeted | 31 | 10 (32%) |
| Hormonal | 0 | 0 |
| Immuno | 74 | 21 (28%) |
| Radio | 61 | 18 (30%) |
| Other | 4 | 1 (25%) |
| None or NA | 0 | 0 |

## Tumor Characteristics

Lung NSCLC / Pan-Cancer

| | Lung NSCLC | Pan-Cancer |
|---|---|---|
| TMB High | 43% | 21% |
| MSI High | 1% | 2% |
| WGD | 77% | 56% |
| Diploid Proportion | 19% | 34% |
| GIE HLA LOH | 27% | 19% |
| GIE Overall | 37% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 2% | 6% |

## Processes Underlying Mutations

- Tobacco: 40%
- APOBEC: 12%
- Chemical exposure: 10%
- DNA damage repair: 7%
- Ageing: 1%
- UV light: 0%
- Unknown: 29%

Lung NSCLC 711 Patients
Pan-Cancer 6790 Patients
Lung

## Mutational Landscape

### Tumor purity
42% / 55%

### Clonal mutation fraction
98% / 95%

### Tumor mutational burden
7.8 → High 43%
4.2 → 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Lung NSCLC | 20,610 | 1,316 | 236 | 347 |
| Pan-Cancer | 10,846 | 983 | 183 | 92 |

Number of variants / Quantile

### Telomere Length
0.79 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
11 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.17 → Instable 1%
0.15 → 2%
MS indels per megabase

### Mean genome ploidy
3 / 2.6

### Aneuploidy Score
21 / 16

### % Copy number alteration
66% / 54%

### % Genome LOH
33% / 24%

## Cancer Driver Landscape

### # Events / Summary — Top cancer drivers

Somatic drivers (49% 6+ / 44%; 51% 1-5 / 54%)

| Gene | Type | Lung NSCLC % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| TP53 | TSG | 68 | 55 | ▲ |
| CDKN2A | TSG | 42 | 24 | ▲ |
| EGFR | ONC | 32 | 5.4 | ▲ |
| KRAS | ONC | 16 | 15 | |
| STK11 | TSG | 16 | 4.1 | ▲ |
| RB1 | TSG | 14 | 11 | |
| KEAP1 | TSG | 9.4 | 2.2 | ▲ |
| PTPRD | TSG | 9.1 | 3 | ▲ |
| MET | ONC | 8.9 | 1.8 | ▲ |
| SMARCA4 | TSG | 8.2 | 2.5 | ▲ |
| TERT | ONC | 7.9 | 13 | |
| ERBB2 | ONC | 7.6 | 5.7 | |
| FOXA1 | ONC | 7.3 | 2.3 | ▲ |
| PIK3CA | ONC | 7 | 13 | ▼ |
| ARID1A | ONC | 6.5 | 6 | |
| BRAF | ONC | 6.5 | 6.2 | |
| MYC | ONC | 6.5 | 5.7 | |
| PTEN | ONC | 6.5 | 14 | ▼ |
| MDM2 | ONC | 6 | 3.3 | |
| SMAD4 | ONC | 5.7 | 5 | |
| EML4_ALK | ONC | 5.6 | 0.7 | ▲ |
| RBM10 | TSG | 4.9 | 1.4 | ▲ |
| CDK4 | ONC | 4.6 | 2 | |
| CCND1 | ONC | 3.8 | 5.6 | |
| CCNE1 | ONC | 3.8 | 2.4 | |
| FGF3 | ONC | 3.8 | 5.2 | |
| APC | TSG | 3.7 | 14 | ▼ |
| FGFR1 | ONC | 3.7 | 3.9 | |
| NF1 | TSG | 3.7 | 5 | |

Oncogenes (39% 3+ / 32%; 52% 1-2 / 50%)
TSGs (4% None; 61% 3+ / 61%; 35% 1-2 / 33%)

701 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

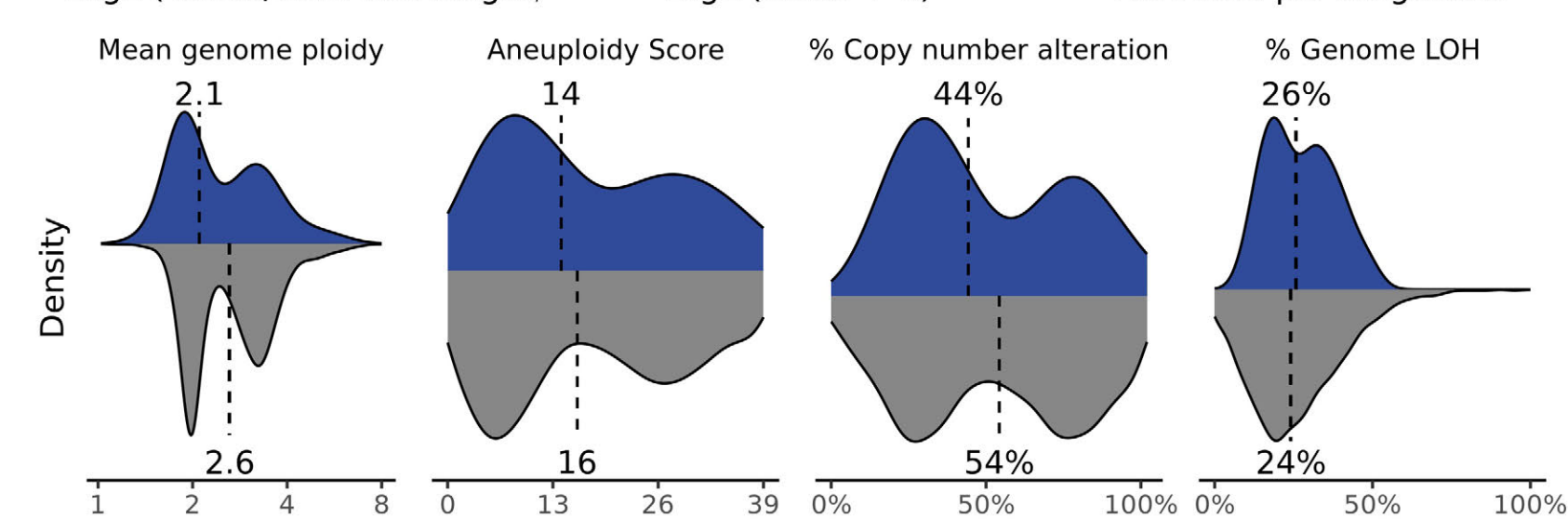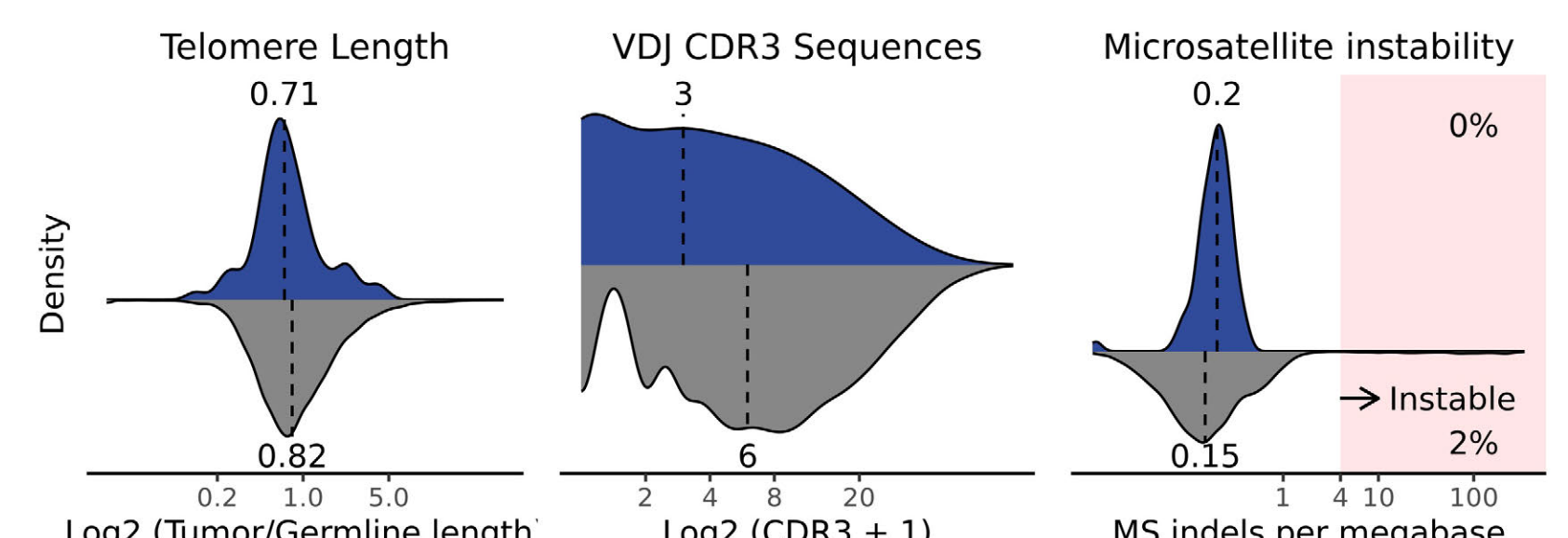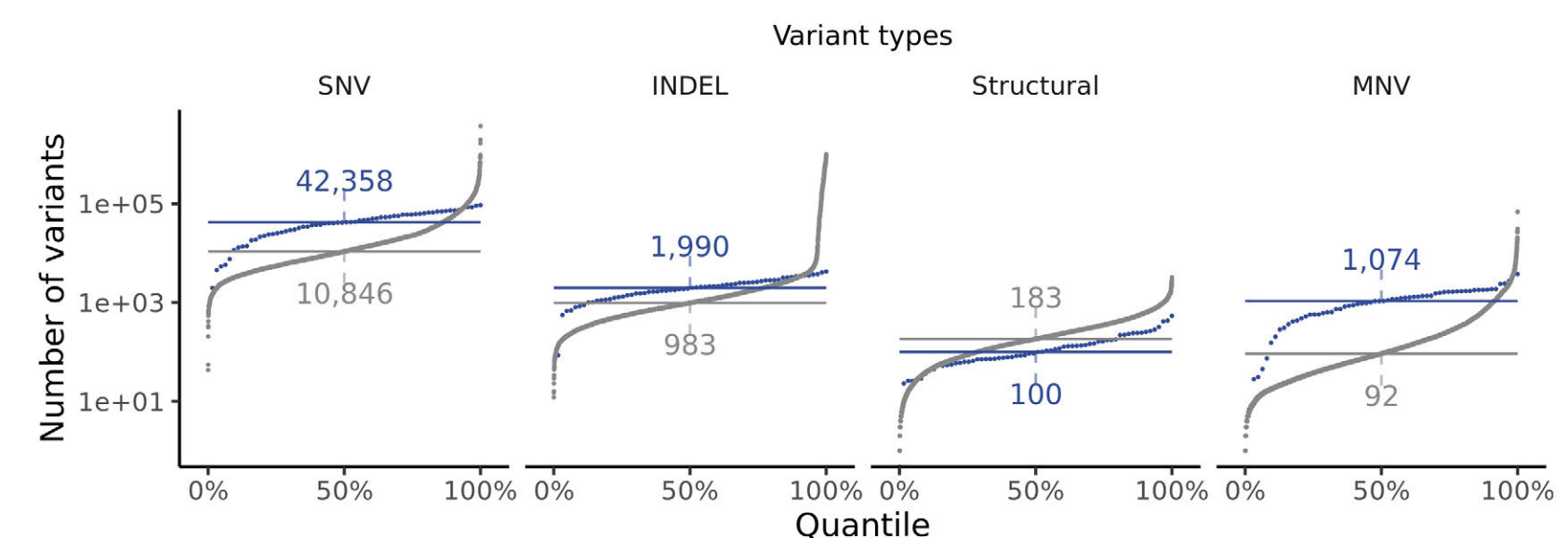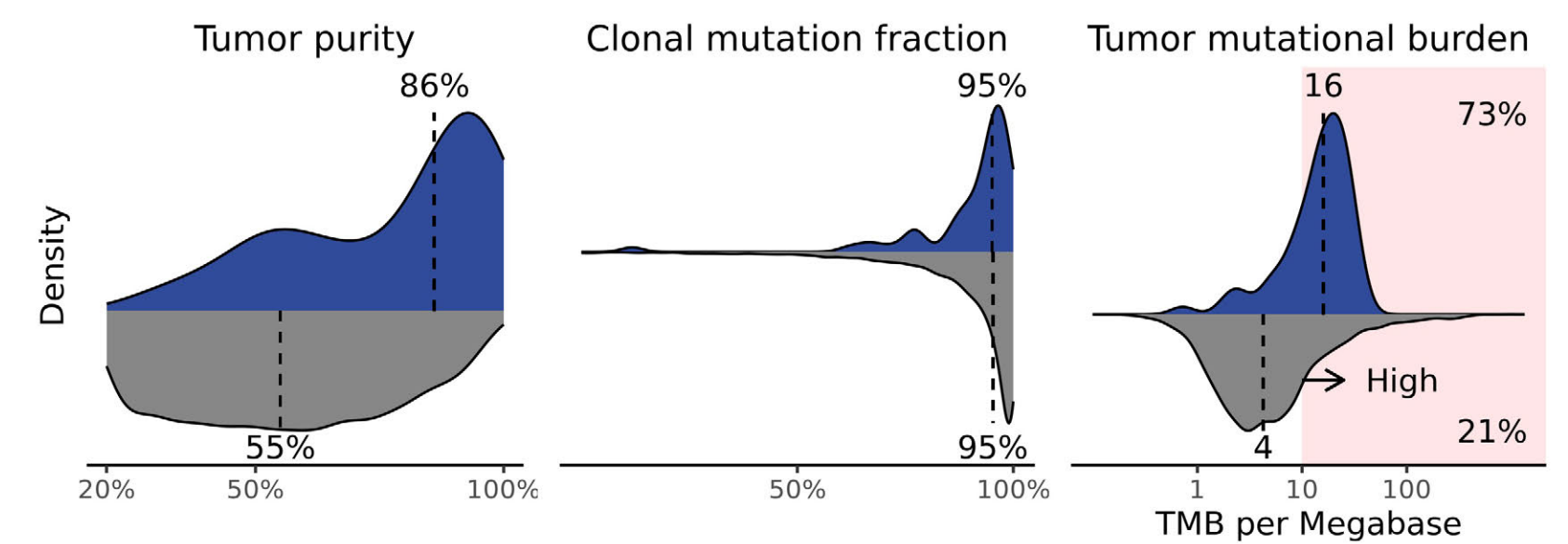## Potentially Actionable Events

### # Events / Summary — Top potential actionable events

Actionable (6% None / 18%; 37% 3+ / 26%; 58% 1-2 / 56%)

| Event | Lung NSCLC % | Pan-Cancer % | Direction |
|---|---|---|---|
| TMB High | 41 | 21 | ▲ |
| CDKN2A | 41 | 24 | ▲ |
| EGFR | 31 | 5.1 | ▲ |
| KRAS | 16 | 14 | |
| MET | 8.3 | 1.7 | ▲ |
| ERBB2 | 7.6 | 5.6 | |
| PIK3CA | 7 | 13 | ▼ |
| PTEN | 6.2 | 13 | ▼ |
| BRAF | 5.9 | 5.9 | |
| EML4 - ALK fusion | 5.2 | 0.6 | ▲ |
| CDK4 | 4.2 | 1.9 | |
| CCND1 | 3.7 | 5.3 | |
| ATM | 3.5 | 3.5 | |
| FGFR1 | 3.5 | 3.8 | |
| CHEK2 | 3.2 | 3 | |
| CTNNB1 | 2.4 | 2.7 | |
| HR deficiency | 1.8 | 5.8 | ▼ |
| KMT2D | 1.8 | 2.9 | |
| NF2 | 1.8 | 1.6 | |
| ERBB4 | 1 | 0.5 | |
| KDM5C | 1 | 0.6 | |
| BRCA2 | 0.8 | 2.4 | |
| CDK12 | 0.8 | 0.9 | |
| Rest FDA | 5.6 | | |
| Rest Repurpose | 8 | | |
| Rest Experimental | 1.1 | | |
| Rest Other | 3.2 | | |

Best treatment option (6% None / 18%; 7% Off / 14%; Exp 5%; 83% FDA / 28%; FDA 36%)

670 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Copy Number Alteration Profile

## Germline Predisposition

### # Events / Summary — Top potential germline drivers

Germline drivers (84% None / 84%; 16% 1+ / 16%)

| Gene | Type | Lung NSCLC % | Pan-Cancer % |
|---|---|---|---|
| CHEK2 | TSG | 3.2 | 3.2 |
| MUTYH | TSG | 2.5 | 1.9 |
| ATM | TSG | 1.5 | 1 |
| TP53 | TSG | 1.1 | 0.5 |
| BRCA1 | TSG | 0.8 | 1.1 |
| MITF | ONC | 0.8 | 0.7 |
| MSH2 | TSG | 0.8 | 1 |
| RAD50 | TSG | 0.7 | 0.5 |
| BRCA2 | TSG | 0.6 | 1.5 |

86 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA Approved | Drug Repurposing | Experimental | Other | None |
|---|---|---|---|---|---|
| WGS | 588 | | 48 | 31 | 39 |
| Comprehensive 521 gene panel | 537 | | 52 | 50 | 63 |
| Targeted 50 gene panel | 319 | 87 | 119 | | 178 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 1.2 | 0.43 | 0.78 | 0.23 | 2.6 |
| Comprehensive 521 gene panel | 1.1 | 0.36 | 0.68 | | 2.3 |
| Targeted 50 gene panel | 0.59 | 0.21 | 0.49 | | 1.4 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
- Fusion 66
- Partial CN Gain 1

Drug Repurposing:
- Fusion 21
- HRD 13
- Partial CN Loss 12
- HMZ Disruption 4
- Splice Site 1

Experimental/Other Guidelines:
- Partial CN Loss 53
- Full CN Loss 13
- Partial CN Gain 4
- Fusion 3
- HMZ Disruption 3

Other:
- Partial CN Loss 51
- Small Variant 1
- HMZ Disruption 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved:
- TMB High 295
- Fusion 66
- Small Variant 35
- Partial CN Gain 1

Drug Repurposing:
- Small Variant 88
- Splice Site 23
- Fusion 21
- HRD 13
- Partial CN Loss 12

Experimental/Other Guidelines:
- Full CN Gain 102
- Partial CN Loss 53
- Small Variant 30
- Full CN Loss 16
- Partial CN Gain 4

Other:
- Partial CN Loss 51
- Small Variant 45
- Splice Site 11
- Full CN Loss 5
- Full CN Gain 2

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Lung Small-Cell Carcinoma

## Cohort Metadata

### Data availability
Number of patients with data

| | |
|---|---|
| WGS | 63 |
| RNASeq | 46 |
| Age, Sex | 54 |
| Biopsy site | 52 |
| Pretreatment | 49 |
| Treatment | 35 |
| Response | 29 |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 26 | 18 (69%) |
| Multiple | 2 | 2 (100%) |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 1 | 0 |
| Radio | 9 | 8 (89%) |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Processes Underlying Mutations

- Tobacco: 45%
- Chemical exposure: 14%
- DNA damage repair: 3%
- APOBEC: 3%
- Ageing: 1%
- UV light: 0%
- Unknown: 34%

Lung SCLC
63 Patients

Pan-Cancer
6790 Patients

Lung

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## Tumor Characteristics

Lung SCLC / Pan-Cancer

| | Lung SCLC | Pan-Cancer |
|---|---|---|
| TMB High | 73% | 21% |
| MSI High | 0% | 2% |
| WGD | 48% | 56% |
| Diploid Proportion | 36% | 34% |
| GIE HLA LOH | 11% | 19% |
| GIE Overall | 25% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
86% / 55%

### Clonal mutation fraction
95% / 95%

### Tumor mutational burden
16 / 73% High
4 / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Lung SCLC | 42,358 | 1,990 | 183 | 1,074 |
| Pan-Cancer | 10,846 | 983 | 100 | 92 |

Number of variants vs Quantile

### Telomere Length
0.71 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
3 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.2 / 0.15
0% / Instable 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
14 / 16

### % Copy number alteration
44% / 54%

### % Genome LOH
26% / 24%

## Copy Number Alteration Profile

(Circos plot with genes: DIAPH2, MEGF6, MYCL, EP300, C11orf1, CDKN1A, IL6ST, CCNE1, KEAP1, LRP1B, ATG7, PIK3CA, MAP3K13, FBXW7, IL7R, LMBRD2, IL6ST, FBXL17, RB1, CDKN1B, PTEN, NOTCH1, CDKN2A, PTPRD, MYC, KMT2C, FGFR1, NMC3, FRYOG1, FOXO1, B2M, IRS2)

## Cancer Driver Landscape

### # Events / Summary

| | Somatic drivers | Lung SCLC (%) | Pan-Cancer (%) |
|---|---|---|---|
| 6+ | 24% | 6+ | 44% |
| 1-5 | 76% | 1-5 | 54% |
| | Oncogenes | | |
| None | | None | 18% |
| 3+ | 59% | 3+ | 32% |
| 1-2 | 6% / 35% | 1-2 | 50% |
| | TSGs | | |
| 3+ | 63% | 3+ | 61% |
| 1-2 | 37% | 1-2 | 33% |

### Summary (Top cancer drivers)

| Gene | Type | Lung SCLC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 95 | 55 | ▲ |
| RB1 | TSG | 81 | 11 | ▲ |
| PTEN | TSG | 11 | 14 | |
| KMT2D | TSG | 9.5 | 2.9 | ▲ |
| MEGF6 | TSG | 7.9 | 0.2 | ▲ |
| NOTCH1 | TSG | 7.9 | 1.3 | ▲ |
| CREBBP | TSG | 6.3 | 1.9 | ▲ |
| MYC | ONC | 6.3 | 5.7 | |
| NCOR1 | TSG | 6.3 | 1.6 | ▲ |
| PIK3CA | ONC | 6.3 | 13 | ▼ |
| ARID1A | TSG | 4.8 | 6 | |
| B2M | TSG | 4.8 | 1.9 | |
| CDKN1B | TSG | 4.8 | 1 | ▲ |
| FAT1 | TSG | 4.8 | 1.5 | ▲ |
| FGFR1 | TSG | 4.8 | 3.9 | |
| IRS2 | ONC | 4.8 | 0.8 | ▲ |
| KDM6A | TSG | 4.8 | 3.7 | |
| MYCL | ONC | 4.8 | 0.5 | ▲ |
| PTPRD | TSG | 4.8 | 3 | |
| BTK | ONC | 3.2 | 0.1 | ▲ |
| CCNE1 | ONC | 3.2 | 2.4 | |
| CD274 | ONC | 3.2 | 0.6 | |
| CDH10 | TSG | 3.2 | 0.6 | |
| EP300 | TSG | 3.2 | 1.3 | |
| IL6ST | ONC | 3.2 | 0.2 | ▲ |
| IL7R | ONC | 3.2 | 0.9 | ▲ |
| KMT2C | TSG | 3.2 | 3.7 | |
| LMBRD2 | ONC | 3.2 | 1 | ▲ |
| MAP3K13 | ONC | 3.2 | 0.4 | ▲ |

Type: TSG / ONC — Lung SCLC (%) / Pan-Cancer (%) — Direction

Top cancer drivers — 63 Patients

Legend: AMPLIFICATION · DELETION · MUTATION

## Potentially Actionable Events

### # Events / Summary

| | Actionable | Lung SCLC | Pan-Cancer |
|---|---|---|---|
| None | 16% | None | 18% |
| 3+ | 6% | 3+ | 26% |
| 1-2 | 78% | 1-2 | 56% |

| | Best treatment option | Lung SCLC | Pan-Cancer |
|---|---|---|---|
| None | 16% | None | 18% |
| Oth | | Oth | 14% |
| Off | 8% | Exp | 5% |
| | | Off | 28% |
| FDA | 73% | FDA | 36% |

### Summary (Top potential actionable events)

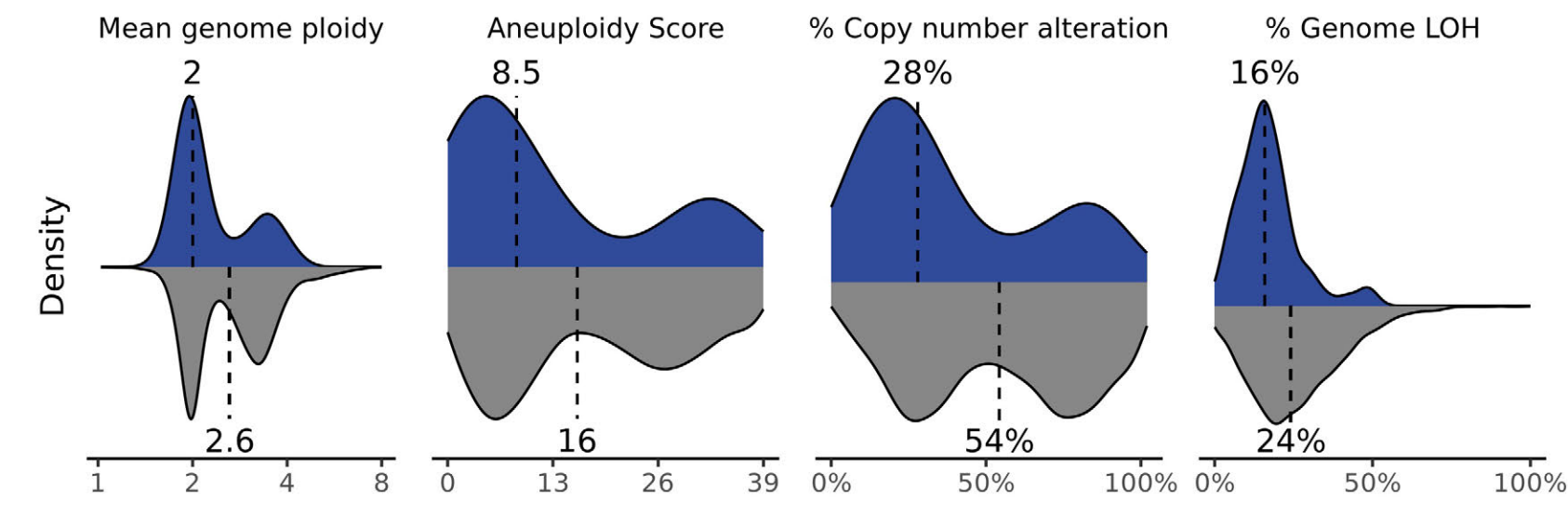| Gene/Event | Lung SCLC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| TMB High | 73 | 21 | |
| PTEN | 11 | 13 | |
| KMT2D | 9.5 | 2.9 | ▲ |
| PIK3CA | 6.3 | 13 | ▼ |
| FGFR1 | 4.8 | 3.8 | |
| CD274 | 3.2 | 0.5 | ▲ |
| AR | 1.6 | 2.8 | |
| BRAF | 1.6 | 5.9 | ▲ |
| BRIP1 | 1.6 | 0.4 | ▲ |
| CDK12 | 1.6 | 0.9 | |
| CDKN2A | 1.6 | 24 | ▼ |
| EML4 - ALK fusion | 1.6 | 0.6 | |
| FGFR3 | 1.6 | 1.2 | |
| KIF5B - RET fusion | 1.6 | 0.1 | ▲ |
| NRAS | 1.6 | 2.6 | |
| TSC1 | 1.6 | 1.1 | |
| TSC2 | 1.6 | 0.8 | |
| UBR5 | 1.6 | 0.3 | ▲ |

Top potential actionable events — 53 Patients

Legend: FDA Approved · Drug Repurposing · Experimental/Other Guidelines · Other

## Germline Predisposition

### # Events / Summary

| | Germline drivers | Lung SCLC | Pan-Cancer |
|---|---|---|---|
| None | 92% | None | 84% |
| 1+ | 8% | 1+ | 16% |

| Gene | Type | Lung SCLC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| PMS2 | TSG | 3.2 | 0.5 | ▲ |
| POLE | TSG | 3.2 | 0.2 | ▲ |
| SDHA | TSG | 1.6 | 0.5 | |

Top potential germline drivers — 5 Patients

Legend: SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved · Drug Repurposing · Other · Experimental/Other Guidelines · None
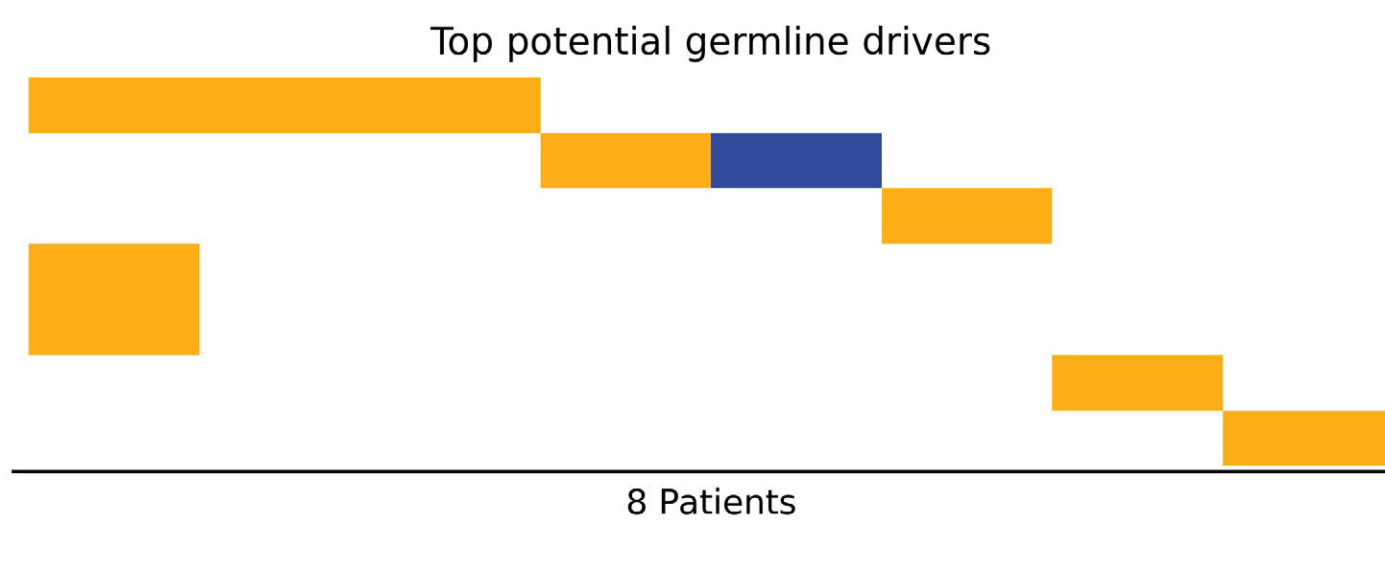
### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Experimental | Other | None |
|---|---|---|---|---|---|
| WGS | 46 | 5 | 2 | | 9 |
| Comprehensive 521 gene panel | 46 | 3 | 3 | | 11 |
| Targeted 50 gene panel | 3 | 6 | 4 | | 50 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | Total |
|---|---|---|---|---|
| WGS | 0.73 | 0.27 | 0.33 | 1.5 |
| Comprehensive 521 gene panel | 0.73 | 0.29 | | 1.3 |
| Targeted 50 gene panel | 0.2 | | | 0.2 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved — (none)
Drug Repurposing: Fusion 2, Partial CN Loss 1
Experimental/Other Guidelines: Partial CN Loss 6
Other: Small Variant 2, Partial CN Loss 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 46
Drug Repurposing: Small Variant 3, Fusion 2, Partial CN Loss 1
Experimental/Other Guidelines: Partial CN Loss 6, Full CN Gain 4, Small Variant 1
Other: Small Variant 12, Full CN Loss 2, Splice Site 2, Partial CN Loss 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Lung Neuroendocrine

## Cohort Metadata

### Data availability
Number of patients with data

- WGS 58
- RNASeq 7
- Age, Sex 8
- Biopsy site 7
- Pretreatment 8
- Treatment 8
- Response 7

### Patients with treatment and response data

Post-biopsy treatment — Responders

- Chemo 2 — 0
- Multiple 1 — 0
- Targeted 3 — 0
- Hormonal 1 — 0
- Immuno 0 — 0
- Radio 1 — 0
- Other 0 — 0
- None or NA 0 — 0

## Tumor Characteristics

Legend: Lung LUNET — Pan-Cancer

| | Lung LUNET | Pan-Cancer |
|---|---|---|
| TMB High | 3% | 21% |
| MSI High | 2% | 2% |
| WGD | 29% | 56% |
| Diploid Proportion | 56% | 34% |
| GIE HLA LOH | 3% | 19% |
| GIE Overall | 7% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
68% / 55%

### Clonal mutation fraction
92% / 95%

### Tumor mutational burden
1.3 / 4.2 — High 3% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Lung LUNET | 3,374 | 220 | 52 | 22 |

### Telomere Length
0.57 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
3 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.032 / 0.15 — Instable 2% / 2%
MS indels per megabase

### Mean genome ploidy
2 / 2.6

### Aneuploidy Score
8.5 / 16

### % Copy number alteration
28% / 54%

### % Genome LOH
16% / 24%

## Processes Underlying Mutations

- Ageing: 18%
- Tobacco: 16%
- Chemical exposure: 13%
- DNA damage repair: 11%
- APOBEC: 3%
- UV light: 1%
- Unknown: 39%

Lung LUNET — 58 Patients
Pan-Cancer — 6790 Patients
Lung

## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

Somatic drivers

| Gene | Type | Lung LUNET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MEN1 | TSG | 22 | 1 | ▲ |
| ARID1A | TSG | 10 | 6 | |
| EIF1AX | ONC | 10 | 0.6 | ▲ |
| HRAS | ONC | 6.9 | 0.7 | ▲ |
| MYCL | ONC | 6.9 | 0.5 | ▲ |
| SF3B1 | ONC | 6.9 | 0.6 | ▲ |
| SMARCE1 | TSG | 6.9 | 0.3 | ▲ |
| ATM | TSG | 5.2 | 2.9 | |
| CCND1 | ONC | 5.2 | 5.6 | |
| CDKN2A | TSG | 5.2 | 25 | ▼ |
| NF1 | TSG | 5.2 | 5 | |
| PTEN | TSG | 5.2 | 14 | ▼ |
| RB1 | TSG | 5.2 | 11 | ▼ |
| SETD2 | TSG | 5.2 | 2.1 | |
| TP53 | TSG | 5.2 | 55 | ▼ |
| BRAF | ONC | 3.4 | 6.2 | |
| CCND2 | ONC | 3.4 | 1.1 | ▲ |
| KMT2C | ONC | 3.4 | 3.7 | |
| KRAS | ONC | 3.4 | 15 | ▼ |
| ANO3_MAML2 | ONC | 1.7 | 0 | |
| AR | ONC | 1.7 | 5.6 | ▼ |
| AXIN2 | TSG | 1.7 | 0.4 | |
| BRAF_BRAF | ONC | 1.7 | 0.1 | ▲ |
| BRD7 | TSG | 1.7 | 0.3 | ▲ |
| BTK | ONC | 1.7 | 0.1 | ▲ |
| CCNE1 | ONC | 1.7 | 2.4 | |
| CHD4 | ONC | 1.7 | 1.2 | |
| CSF3R | ONC | 1.7 | 0.1 | ▲ |
| DLG2_MAML2 | ONC | 1.7 | 0 | |

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

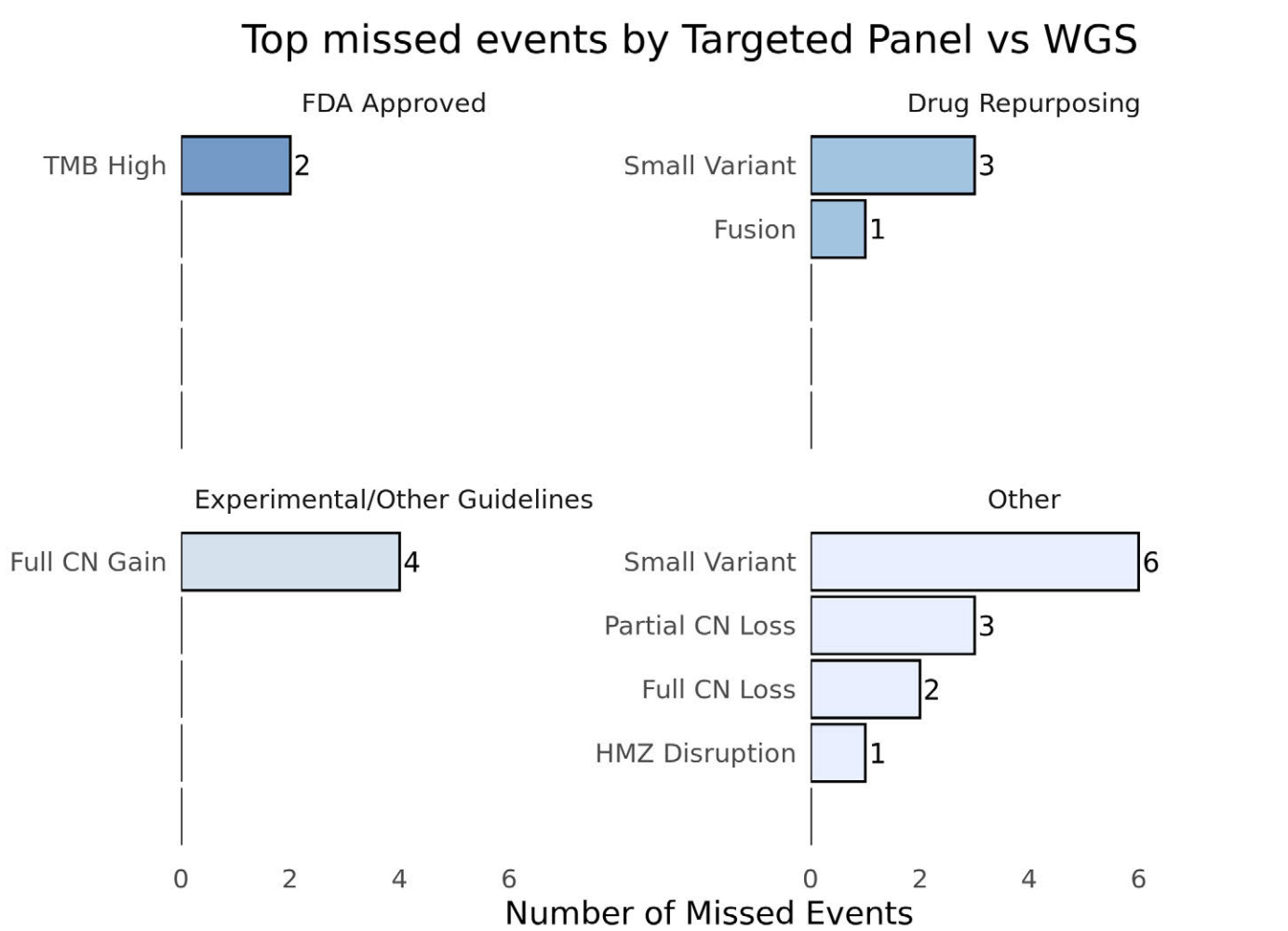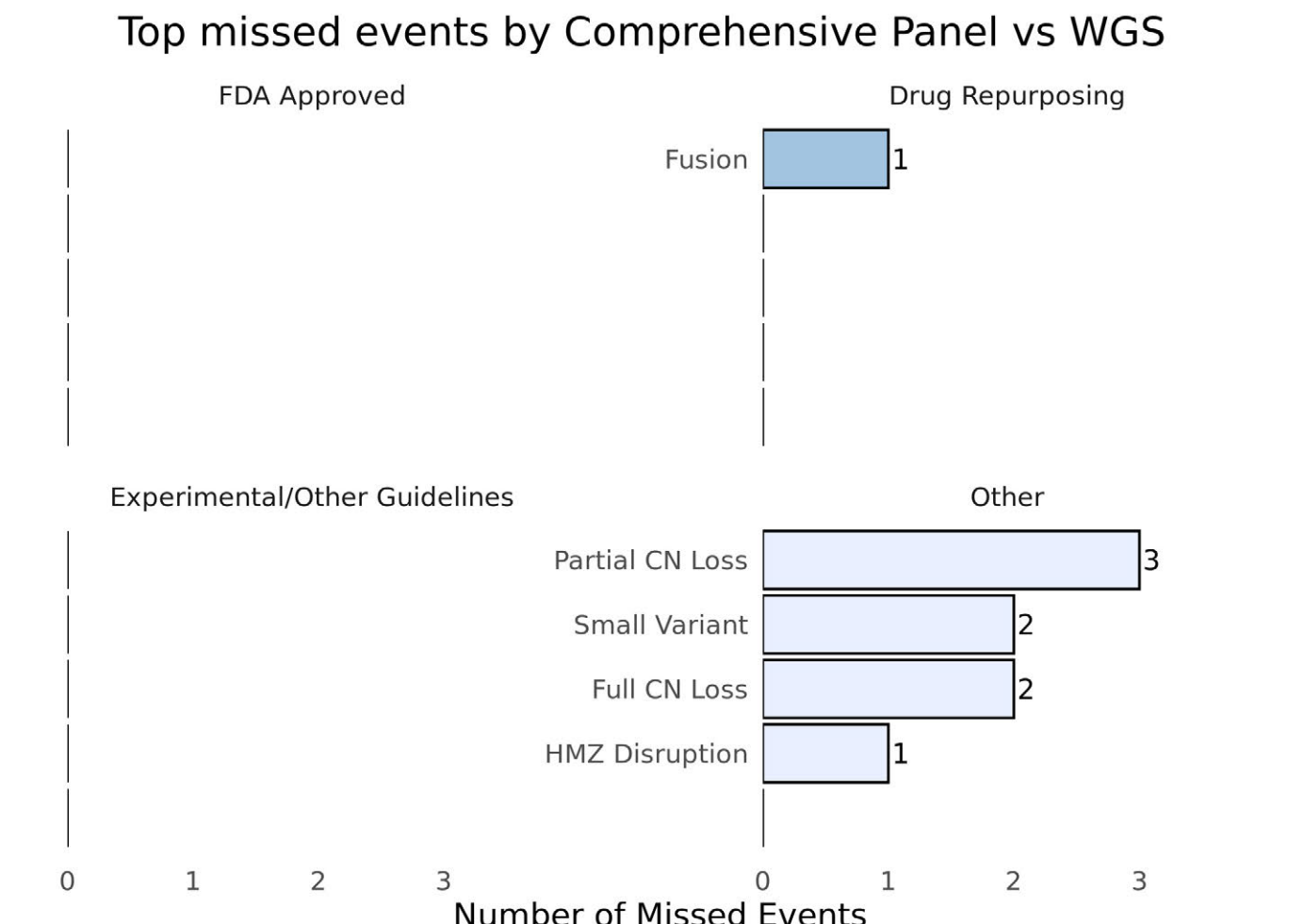Top cancer drivers — 39 Patients

## Potentially Actionable Events

### # Events / Summary

| Gene/Event | Lung LUNET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| ATM | 5.2 | 3.5 | |
| CCND1 | 5.2 | 5.3 | |
| CDKN2A | 5.2 | 24 | ▼ |
| HRAS | 5.2 | 0.6 | ▲ |
| PTEN | 5.2 | 13 | ▼ |
| BRAF | 3.4 | 5.9 | |
| KRAS | 3.4 | 14 | ▼ |
| TMB High | 3.4 | 21 | ▼ |
| BRAF - BRAF fusion | 1.7 | 0.1 | ▲ |
| BRCA1 | 1.7 | 1.3 | |
| KDM5C | 1.7 | 0.6 | ▲ |
| KDR | 1.7 | 0.1 | ▲ |
| KMT2D | 1.7 | 2.9 | |
| MSI High | 1.7 | 3.1 | |
| MTOR | 1.7 | 1.1 | |
| PIK3CA | 1.7 | 13 | ▼ |
| UBR5 | 1.7 | 0.3 | ▲ |

Top potential actionable events — 22 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events / Summary

Germline drivers

| Gene | Type | Lung LUNET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MITF | ONC | 5.2 | 0.7 | ▲ |
| MEN1 | TSG | 3.4 | 0.1 | ▲ |
| ATM | TSG | 1.7 | 1 | |
| BRCA1 | TSG | 1.7 | 1.1 | |
| FLCN | TSG | 1.7 | 0.1 | ▲ |
| NF1 | TSG | 1.7 | 0.2 | ▲ |
| TP53 | TSG | 1.7 | 0.5 | ▲ |

Top potential germline drivers — 8 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA | Drug Rep | Exp | Other | None |
|---|---|---|---|---|---|
| WGS | 4 | 7 | 5 | 6 | 36 |
| Comprehensive 521 gene panel | 4 | 7 | 5 | 4 | 38 |
| Targeted 50 gene panel | 3 | 5 | 2 | | 47 |

### Average number of identified potentially actionable events identified by test strategy

- WGS — 0.26 / 0.6
- Comprehensive 521 gene panel — 0.4
- Targeted 50 gene panel — 0.2

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved / Drug Repurposing
- Fusion 1

Experimental/Other Guidelines / Other
- Partial CN Loss 3
- Small Variant 2
- Full CN Loss 2
- HMZ Disruption 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved
- TMB High 2

Drug Repurposing
- Small Variant 3
- Fusion 1

Experimental/Other Guidelines
- Full CN Gain 4

Other
- Small Variant 6
- Partial CN Loss 3
- Full CN Loss 2
- HMZ Disruption 1

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementary-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red); moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).
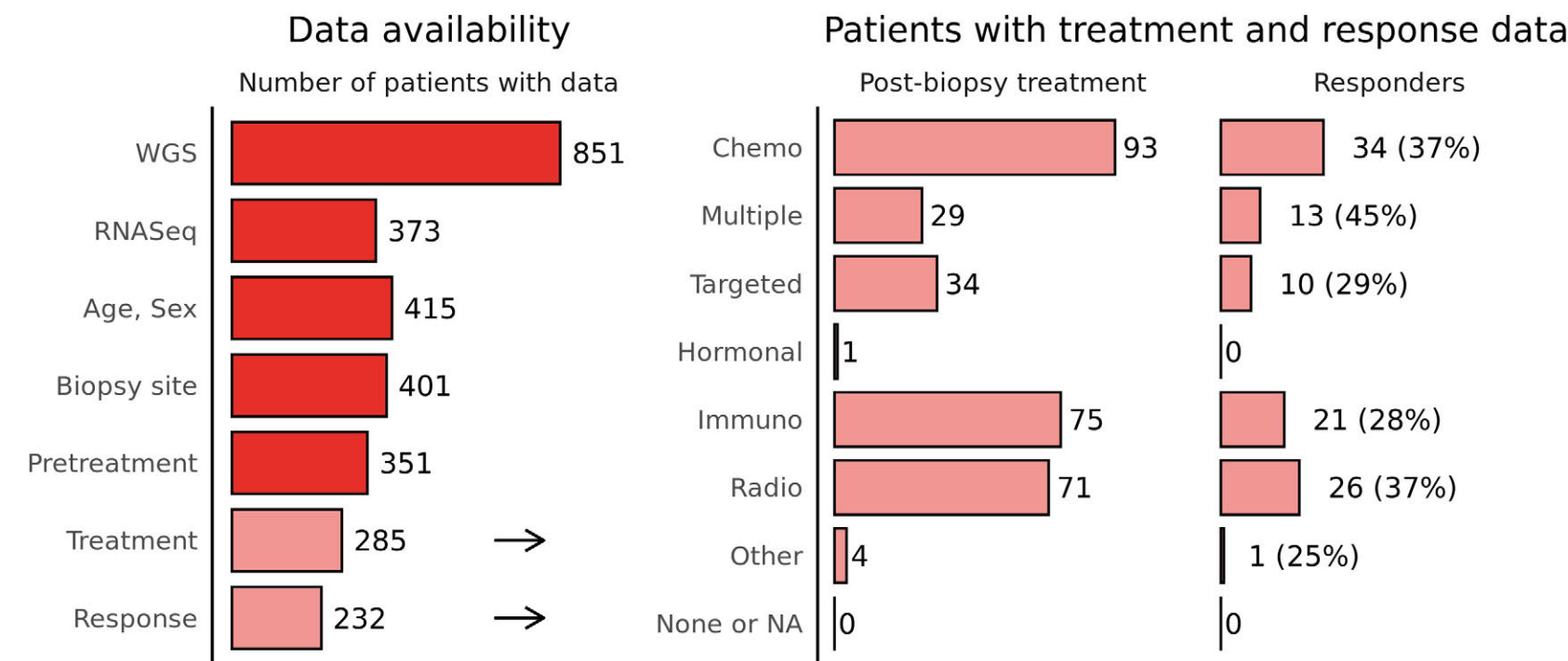
Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: LUNET
DOIDs included: 169, 1324, 5410, 50872
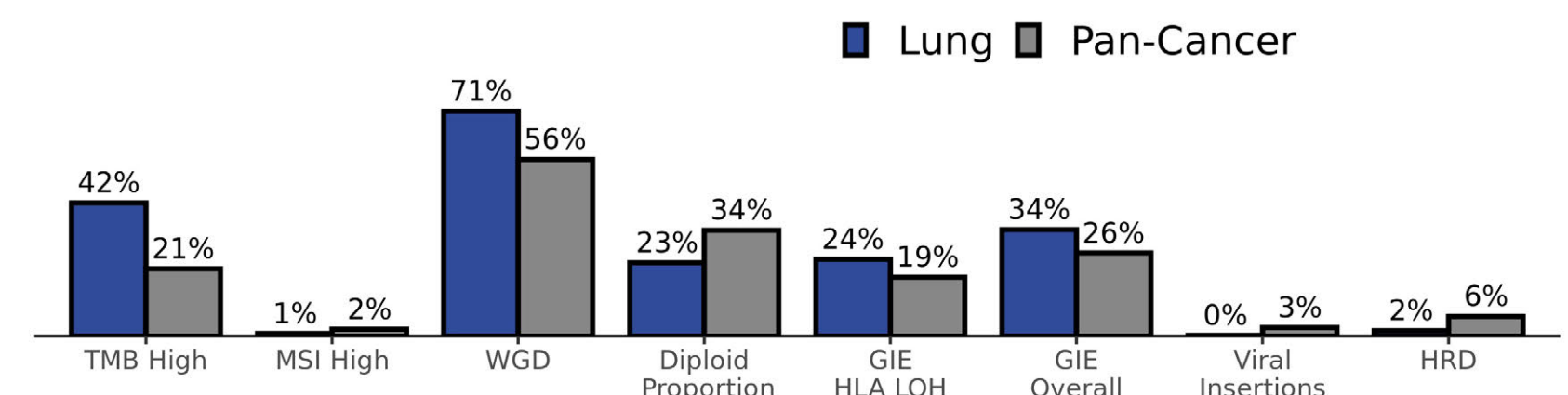Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for partial gene events with: min copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (Homozygous) Disruptions, Viral inserts, HLA type assumed not captured by panels.
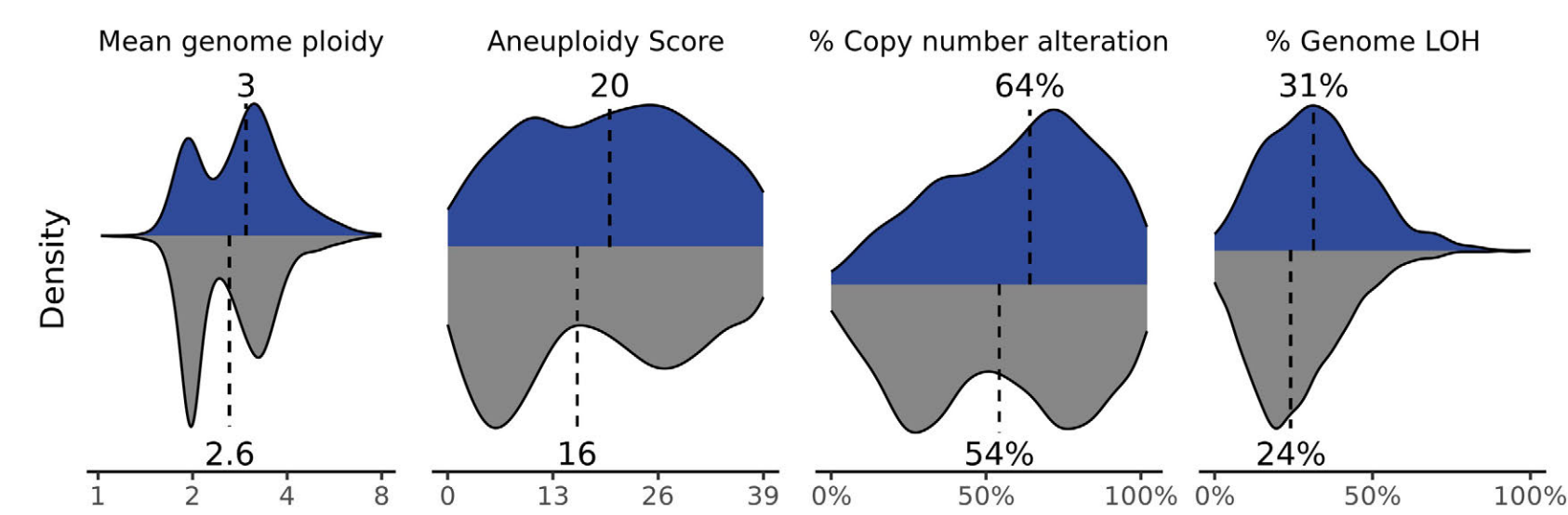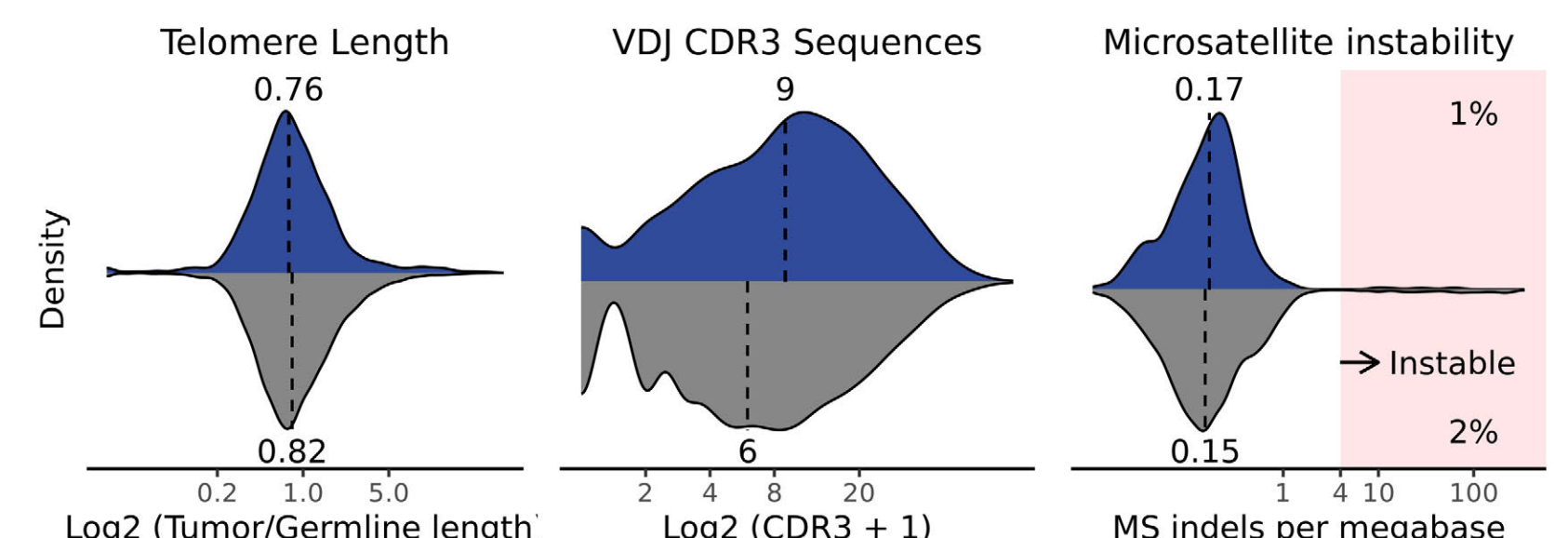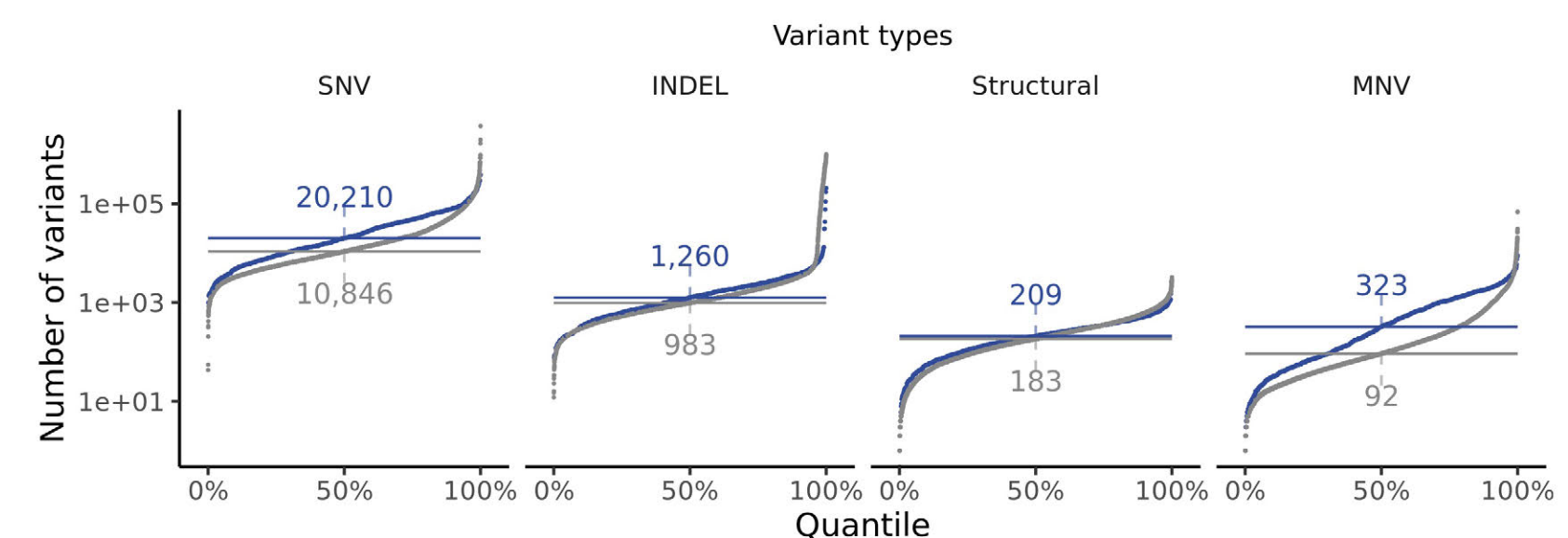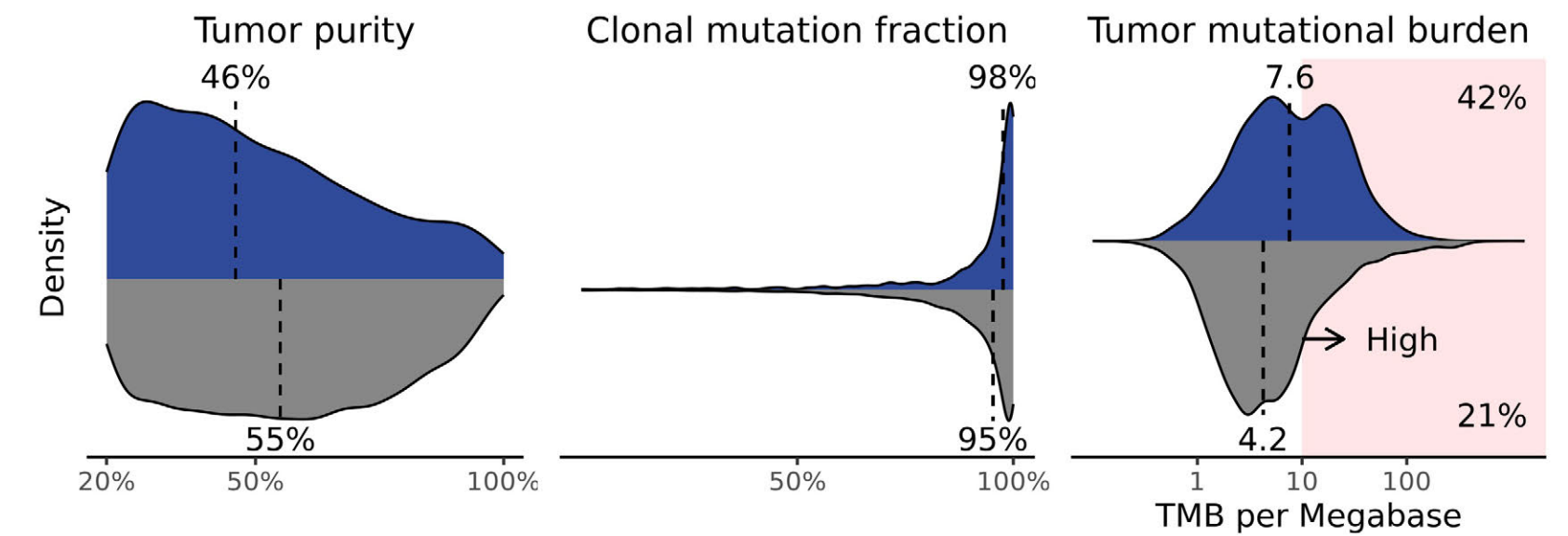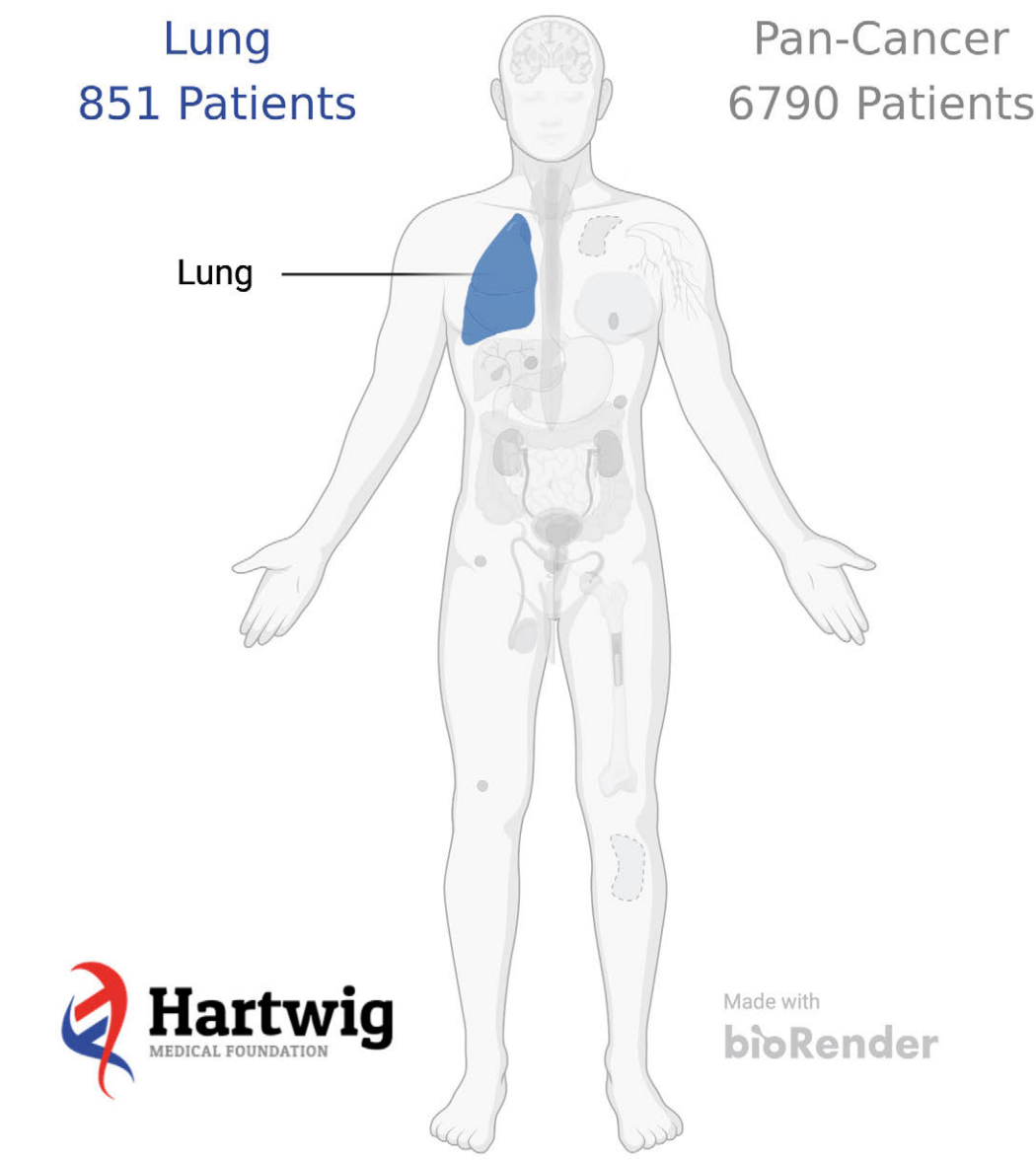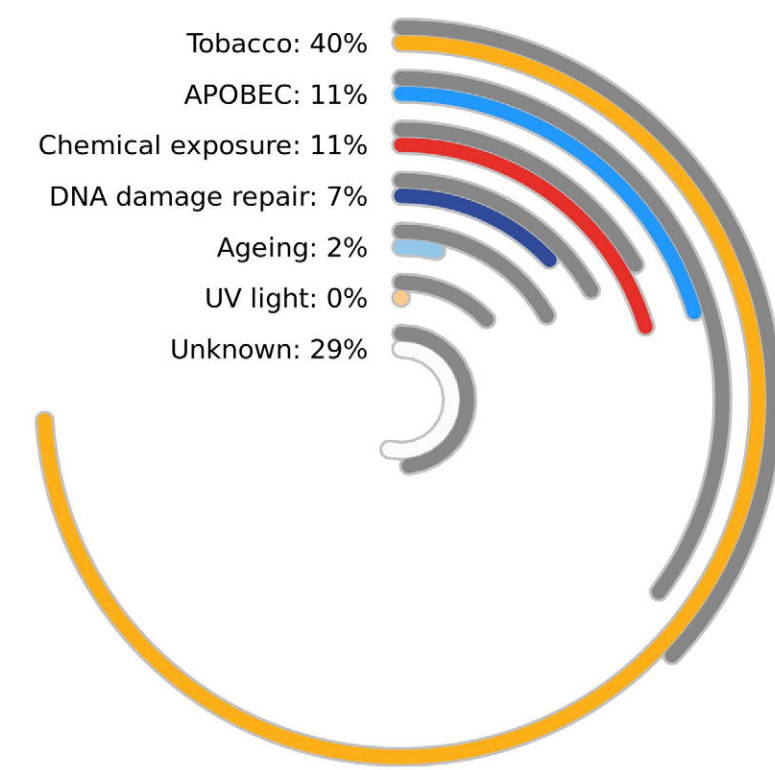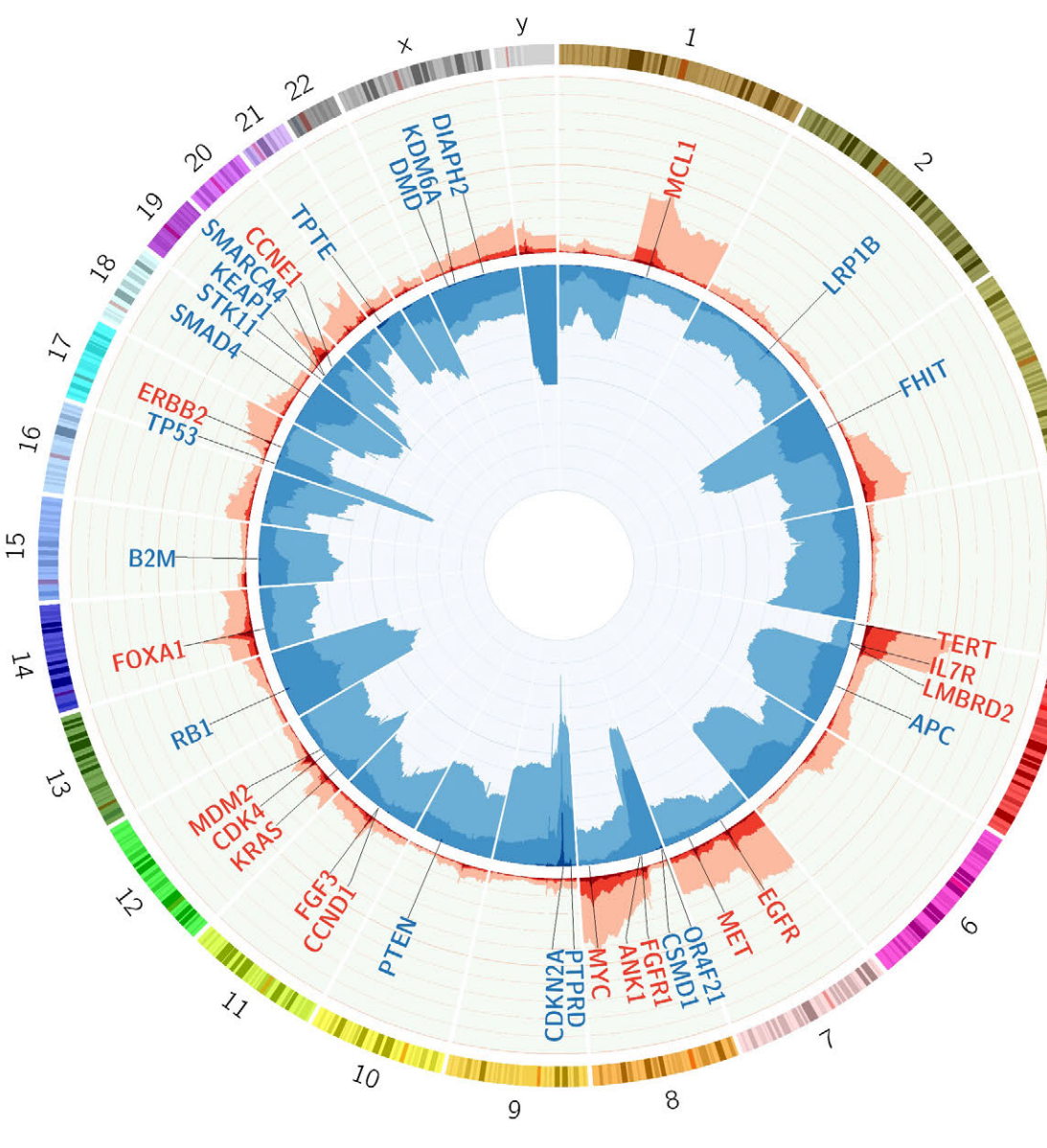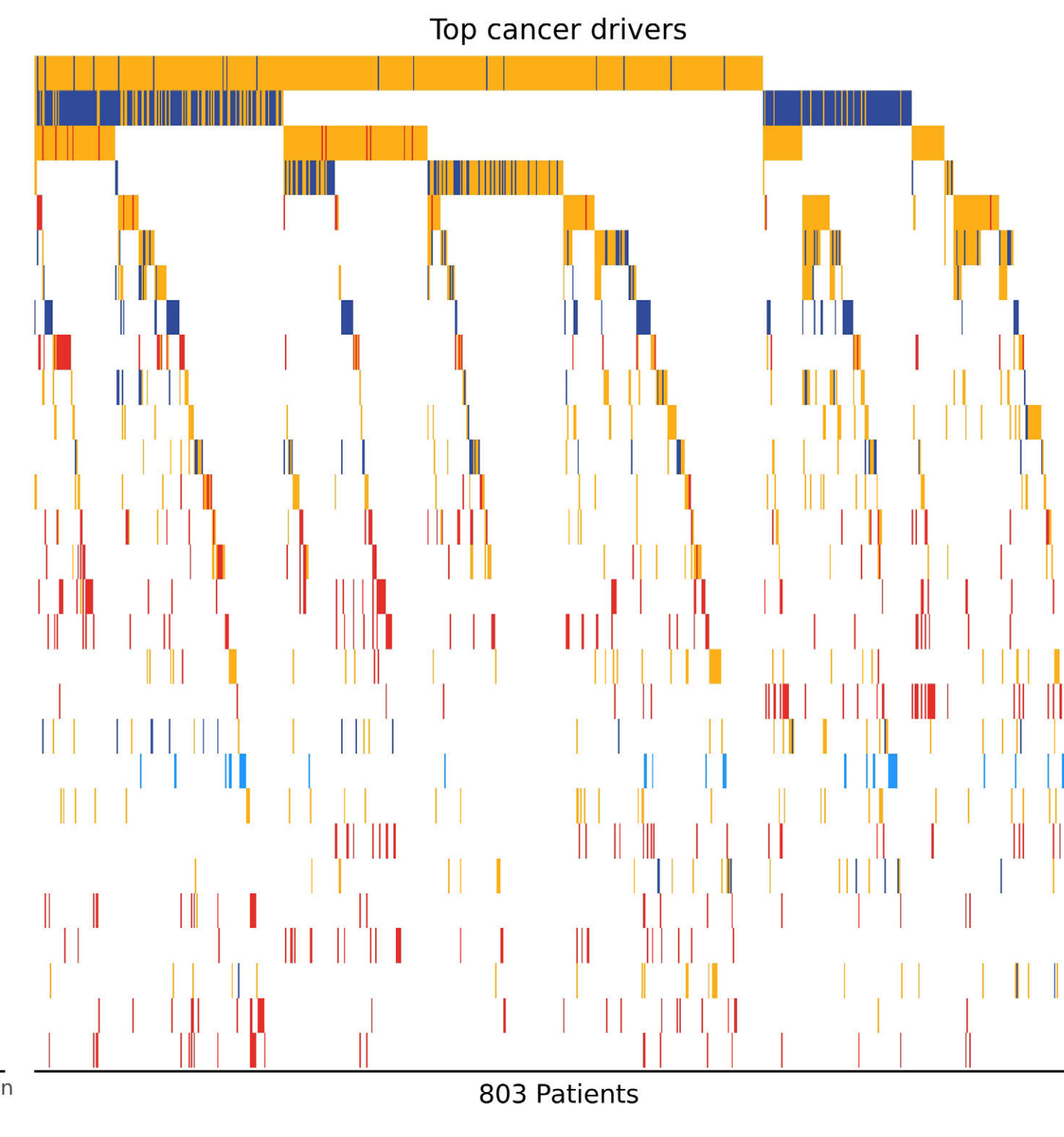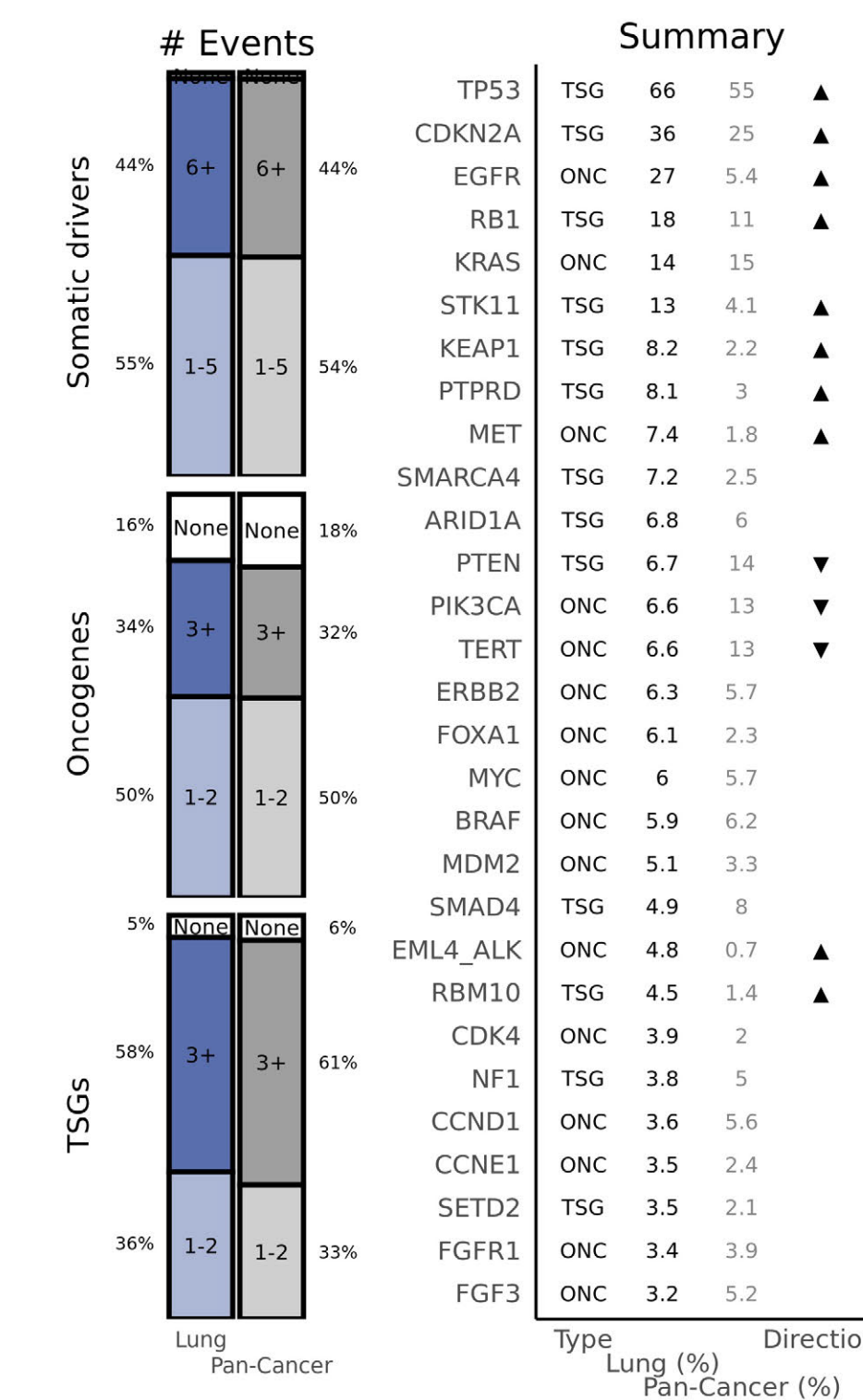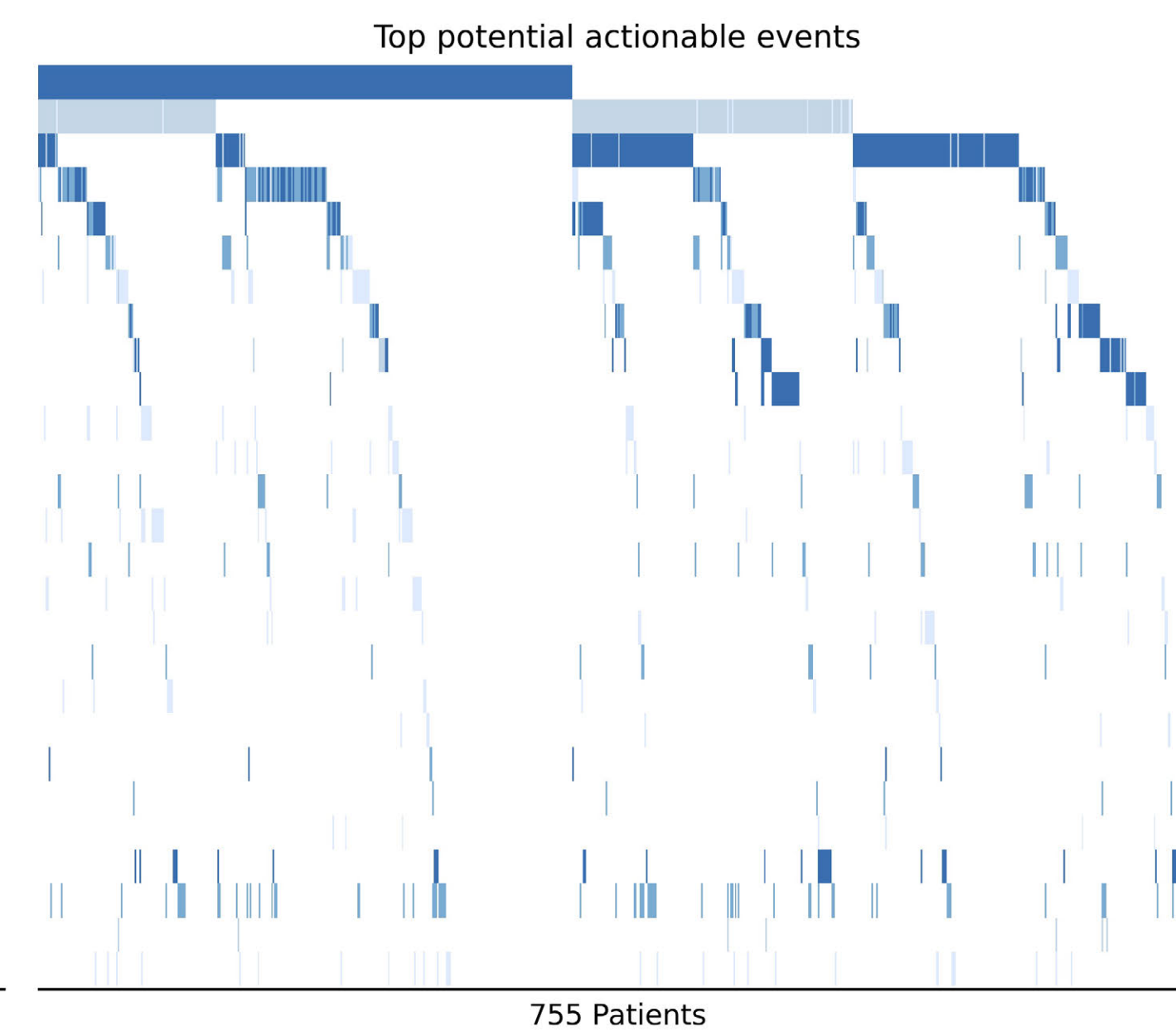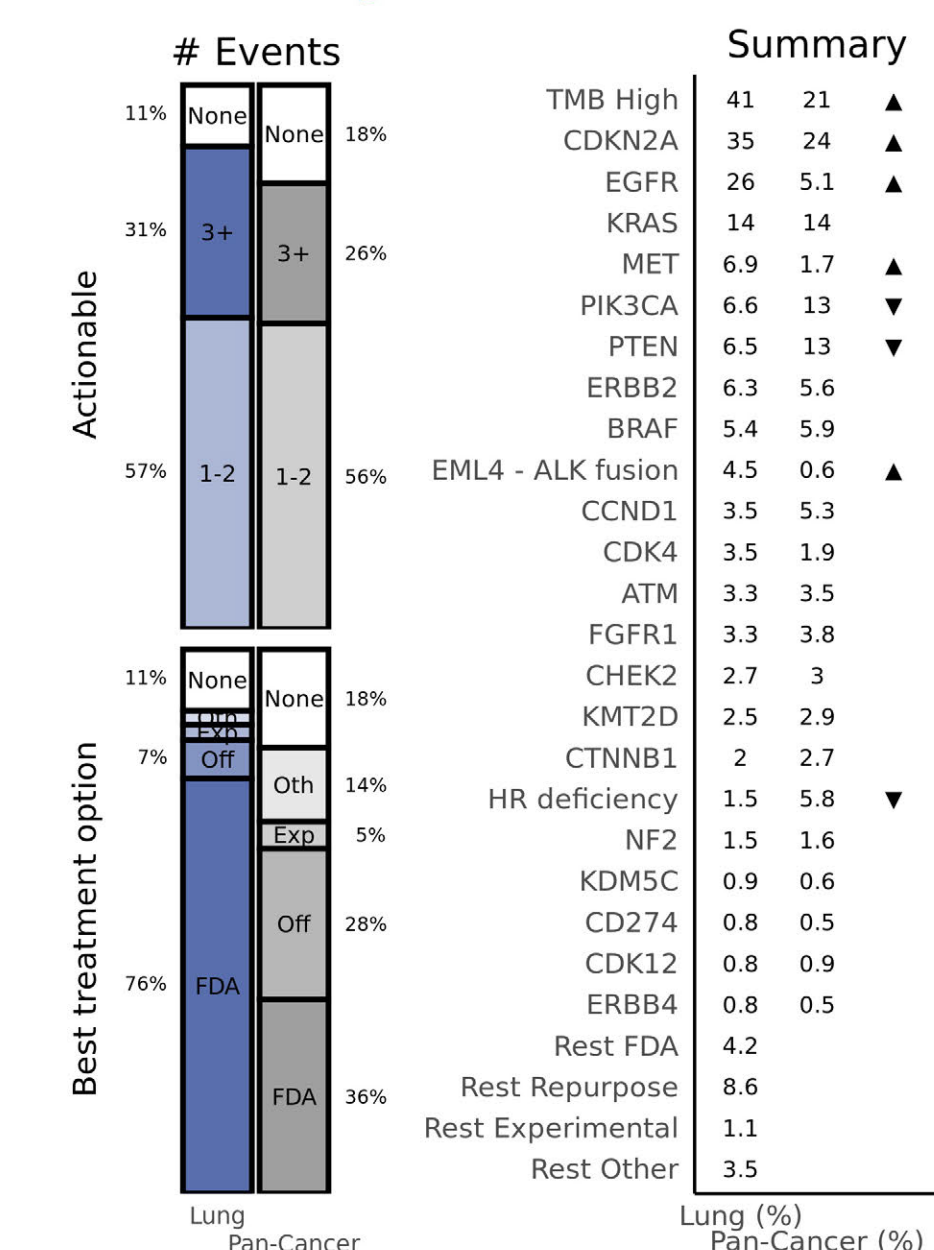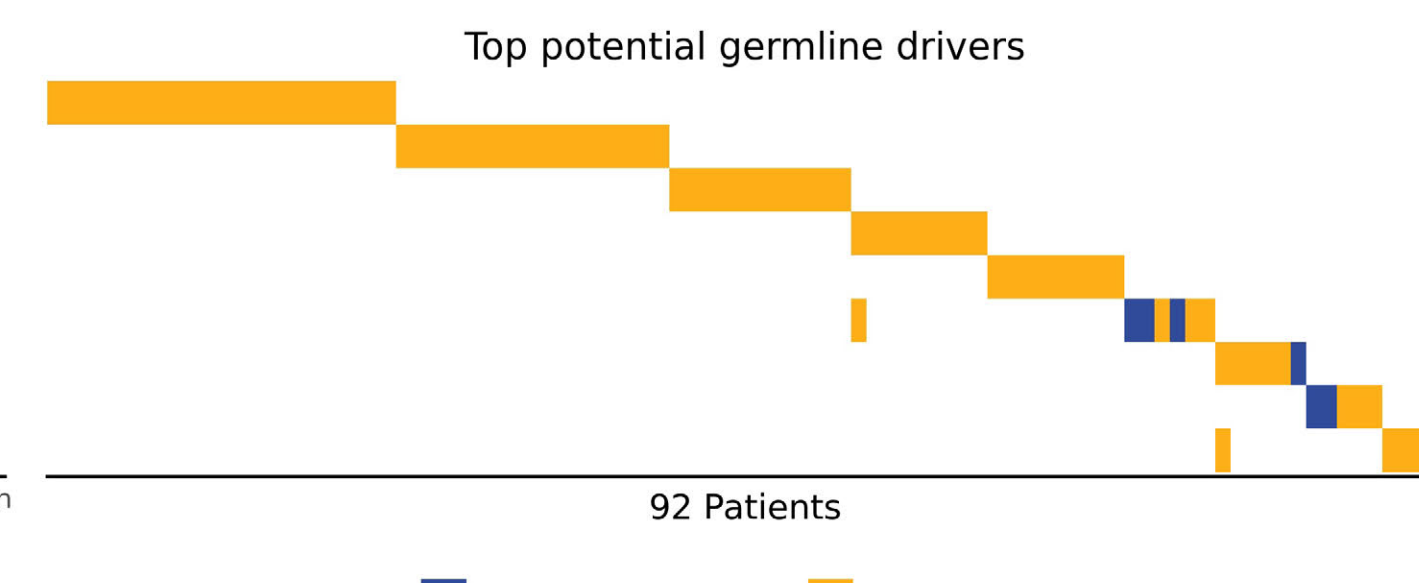** See documentation for further details on the WGS vs Panel coverage study.

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# The Genomic And Actionability Landscape Of Lung Cancer

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 851 |
| RNASeq | 373 |
| Age, Sex | 415 |
| Biopsy site | 401 |
| Pretreatment | 351 |
| Treatment | 285 → |
| Response | 232 → |

**Patients with treatment and response data**

Post-biopsy treatment | Responders

| | Post-biopsy | Responders |
|---|---|---|
| Chemo | 93 | 34 (37%) |
| Multiple | 29 | 13 (45%) |
| Targeted | 34 | 10 (29%) |
| Hormonal | 1 | 0 |
| Immuno | 75 | 21 (28%) |
| Radio | 71 | 26 (37%) |
| Other | 4 | 1 (25%) |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Lung (dark blue), Pan-Cancer (grey)

| | Lung | Pan-Cancer |
|---|---|---|
| TMB High | 42% | 21% |
| MSI High | 1% | 2% |
| WGD | 71% | 56% |
| Diploid Proportion | 23% | 34% |
| GIE HLA LOH | 24% | 19% |
| GIE Overall | 34% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 2% | 6% |

## Mutational Landscape

**Tumor purity** 46% / 55%
**Clonal mutation fraction** 98% / 95%
**Tumor mutational burden** 7.6 (42%) / 4.2 (21%) — High; TMB per Megabase

**Variant types**

Number of variants vs Quantile

| | Lung | Pan-Cancer |
|---|---|---|
| SNV | 20,210 | 10,846 |
| INDEL | 1,260 | 983 |
| Structural | 209 | 183 |
| MNV | 323 | 92 |

**Telomere Length** 0.76 / 0.82 — Log2 (Tumor/Germline length)
**VDJ CDR3 Sequences** 9 / 6 — Log2 (CDR3 + 1)
**Microsatellite instability** 0.17 (1%) / 0.15 (2%) — Instable; MS indels per megabase

**Mean genome ploidy** 3 / 2.6
**Aneuploidy Score** 20 / 16
**% Copy number alteration** 64% / 54%
**% Genome LOH** 31% / 24%

## Processes Underlying Mutations

| Process | % |
|---|---|
| Tobacco | 40% |
| APOBEC | 11% |
| Chemical exposure | 11% |
| DNA damage repair | 7% |
| Ageing | 2% |
| UV light | 0% |
| Unknown | 29% |

**Lung** 851 Patients
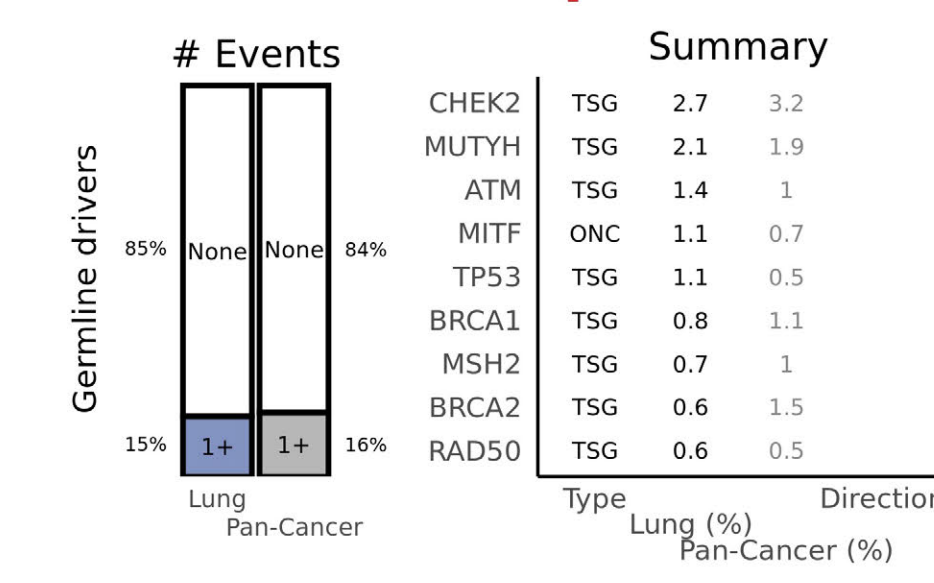**Pan-Cancer** 6790 Patients

Lung

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## Copy Number Alteration Profile

## Cancer Driver Landscape

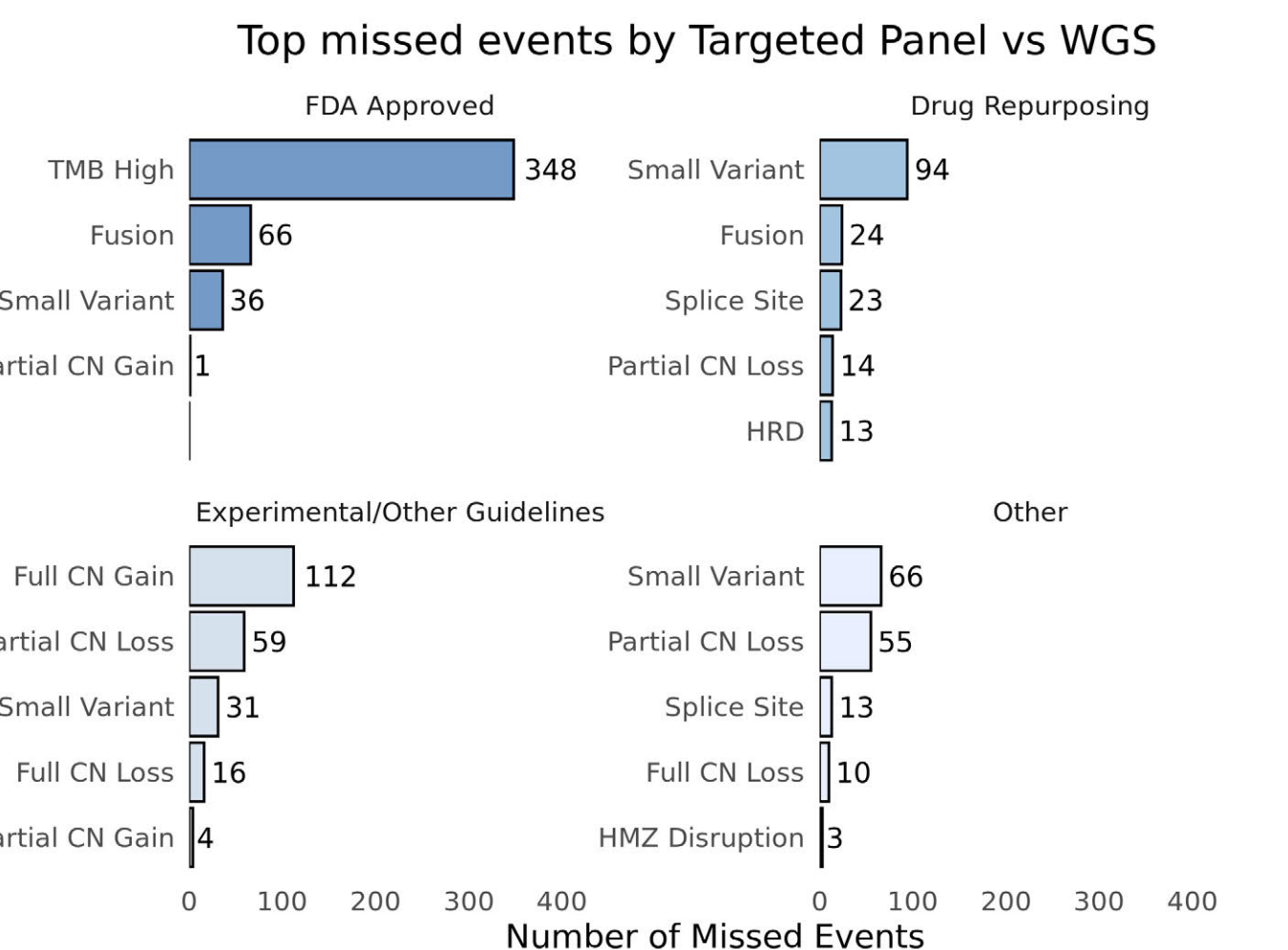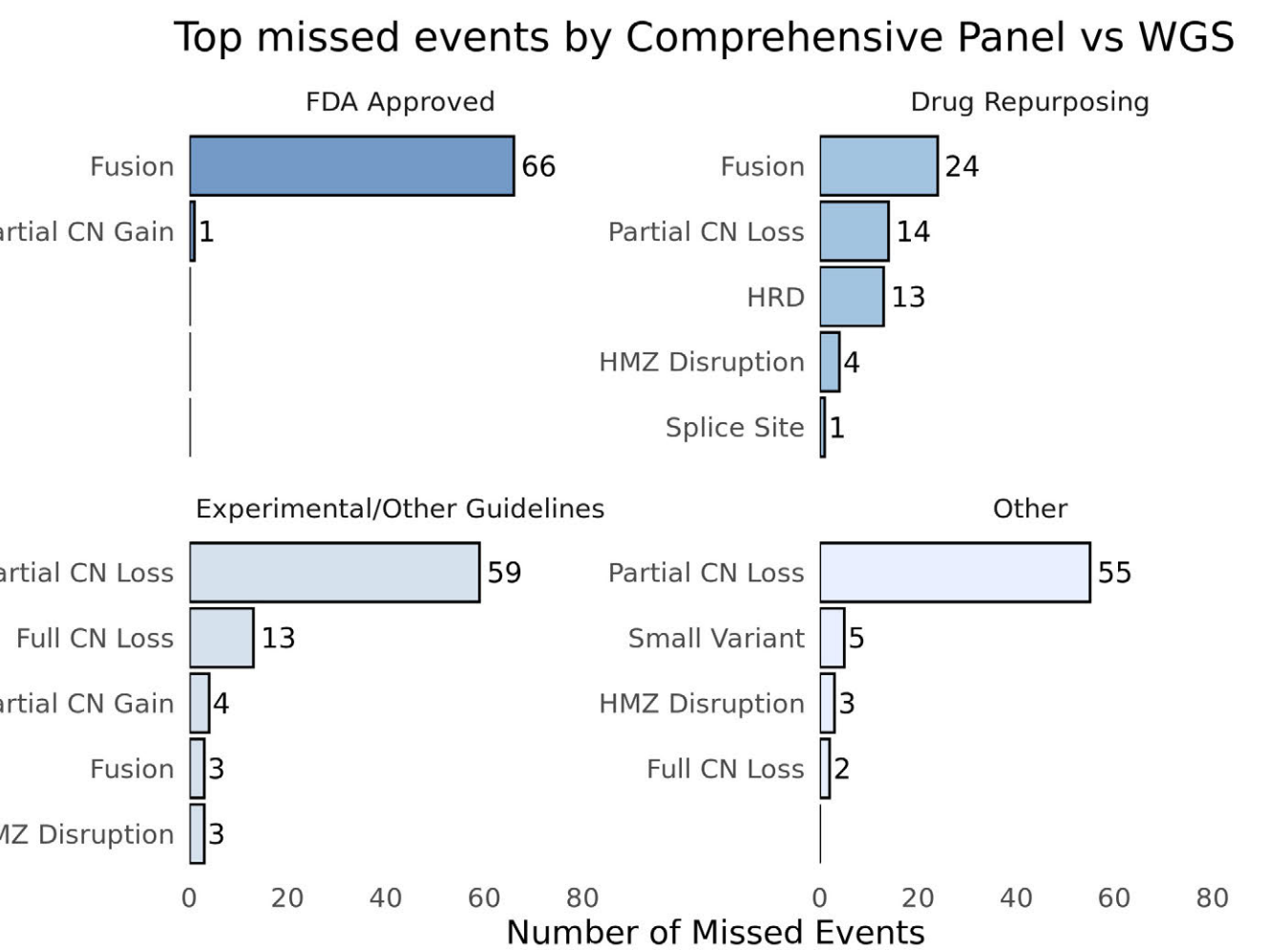### # Events / Summary

**Somatic drivers:** 44% 6+ / 6+ 44%; 55% 1-5 / 1-5 54%
**Oncogenes:** 16% None / None 18%; 34% 3+ / 3+ 32%; 50% 1-2 / 1-2 50%
**TSGs:** 5% None / None 5%; 58% 3+ / 3+ 61%; 36% 1-2 / 1-2 33%

| Gene | Type | Lung (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 66 | 55 | ▲ |
| CDKN2A | TSG | 36 | 25 | ▲ |
| EGFR | ONC | 27 | 5.4 | ▲ |
| RB1 | TSG | 18 | 11 | ▲ |
| KRAS | ONC | 14 | 15 | |
| STK11 | TSG | 13 | 4.1 | ▲ |
| KEAP1 | TSG | 8.2 | 2.2 | ▲ |
| PTPRD | TSG | 8.1 | 3 | ▲ |
| MET | ONC | 7.4 | 1.8 | ▲ |
| SMARCA4 | TSG | 7.2 | 2.5 | |
| ARID1A | TSG | 6.8 | 6 | |
| PTEN | TSG | 6.7 | 14 | ▼ |
| PIK3CA | ONC | 6.6 | 13 | ▼ |
| TERT | ONC | 6.6 | 13 | ▼ |
| ERBB2 | ONC | 6.3 | 5.7 | |
| FOXA1 | ONC | 6.1 | 2.3 | |
| MYC | ONC | 6 | 5.7 | |
| BRAF | ONC | 5.9 | 6.2 | |
| MDM2 | ONC | 5.1 | 3.3 | |
| SMAD4 | ONC | 5 | 3.2 | |
| EML4_ALK | ONC | 4.8 | 0.7 | ▲ |
| RBM10 | TSG | 4.5 | 1.4 | ▲ |
| CDK4 | ONC | 3.9 | 2 | |
| NF1 | TSG | 3.8 | 5 | |
| CCND1 | ONC | 3.6 | 5.6 | |
| CCNE1 | ONC | 3.5 | 2.4 | |
| SETD2 | TSG | 3.5 | 2.1 | |
| FGFR1 | ONC | 3.4 | 3.9 | |
| FGF3 | ONC | 3.2 | 5.2 | |

Top cancer drivers — 803 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange), FUSION (light blue)

## Potentially Actionable Events

### # Events / Summary

**Actionable:** 11% None / None 18%; 31% 3+ / 3+ 26%; 57% 1-2 / 1-2 56%
**Best treatment option:** 11% None / None 18%; 7% Off / Oth 14%; Exp; 5% / 28% Off; 76% FDA / FDA 36%

| Event | Lung (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| TMB High | 41 | 21 | ▲ |
| CDKN2A | 35 | 24 | ▲ |
| EGFR | 26 | 5.1 | ▲ |
| KRAS | 14 | 14 | |
| MET | 6.9 | 1.7 | ▲ |
| PIK3CA | 6.6 | 13 | ▼ |
| PTEN | 6.5 | 13 | ▼ |
| ERBB2 | 6.3 | 5.7 | |
| BRAF | 5.4 | 5.9 | |
| EML4 - ALK fusion | 4.5 | 0.6 | ▲ |
| CCND1 | 3.5 | 5.3 | |
| CDK4 | 3.5 | 1.9 | |
| ATM | 3.3 | 3.5 | |
| FGFR1 | 3.3 | 3.8 | |
| CHEK2 | 2.7 | 3 | |
| KMT2D | 2.5 | 2.9 | |
| CTNNB1 | 2 | 2.7 | |
| HR deficiency | 1.5 | 5.8 | ▼ |
| NF2 | 1.5 | 1.6 | |
| KDM5C | 0.9 | 0.6 | |
| CD274 | 0.8 | 0.5 | |
| CDK12 | 0.8 | 0.9 | |
| ERBB4 | 0.8 | 0.5 | |
| Rest FDA | 4.2 | | |
| Rest Repurpose | 8.6 | | |
| Rest Experimental | 1.1 | | |
| Rest Other | 3.5 | | |

Top potential actionable events — 755 Patients

Legend: FDA Approved (dark blue), Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

**Germline drivers:** 85% None / None 84%; 15% 1+ / 1+ 16%

| Gene | Type | Lung (%) | Pan-Cancer (%) |
|---|---|---|---|
| CHEK2 | TSG | 2.7 | 3.2 |
| MUTYH | TSG | 2.1 | 1.9 |
| ATM | TSG | 1.4 | 1 |
| MITF | ONC | 1.1 | 0.7 |
| TP53 | TSG | 1.1 | 0.5 |
| BRCA1 | TSG | 0.8 | 1.1 |
| MSH2 | TSG | 0.7 | 1 |
| BRCA2 | TSG | 0.6 | 1.5 |
| RAD50 | TSG | 0.6 | 0.5 |

Top potential germline drivers — 92 Patients

Legend: STRUCTURAL_VARIANT (blue), SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Experimental | Other/None |
|---|---|---|---|---|
| WGS | 645 | 62 | 39 | 92 |
| Comprehensive 521 gene panel | 594 | 63 | 57 | 120 |
| Targeted 50 gene panel | 324 | 97 | 126 | 290 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | Total |
|---|---|---|---|---|
| WGS | 1 | 0.39 | 0.69 | 0.24 → 2.4 |
| Comprehensive 521 gene panel | 0.95 | 0.33 | 0.59 | → 2 |
| Targeted 50 gene panel | 0.5 | 0.42 | | 1.2 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
| Event | Count |
|---|---|
| Fusion | 66 |
| Partial CN Gain | 1 |

**Drug Repurposing**
| Event | Count |
|---|---|
| Fusion | 24 |
| Partial CN Loss | 14 |
| HRD | 13 |
| HMZ Disruption | 4 |
| Splice Site | 1 |

**Experimental/Other Guidelines**
| Event | Count |
|---|---|
| Partial CN Loss | 59 |
| Full CN Loss | 13 |
| Partial CN Gain | 4 |
| Fusion | 3 |
| HMZ Disruption | 3 |

**Other**
| Event | Count |
|---|---|
| Partial CN Loss | 55 |
| Small Variant | 5 |
| HMZ Disruption | 3 |
| Full CN Loss | 2 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
| Event | Count |
|---|---|
| TMB High | 348 |
| Fusion | 66 |
| Small Variant | 36 |
| Partial CN Gain | 1 |

**Drug Repurposing**
| Event | Count |
|---|---|
| Small Variant | 94 |
| Fusion | 24 |
| Splice Site | 23 |
| Partial CN Loss | 14 |
| HRD | 13 |

**Experimental/Other Guidelines**
| Event | Count |
|---|---|
| Full CN Gain | 112 |
| Partial CN Loss | 59 |
| Small Variant | 31 |
| Full CN Loss | 16 |
| Partial CN Gain | 4 |

**Other**
| Event | Count |
|---|---|
| Small Variant | 66 |
| Partial CN Loss | 55 |
| Splice Site | 13 |
| Full CN Loss | 10 |
| HMZ Disruption | 3 |

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
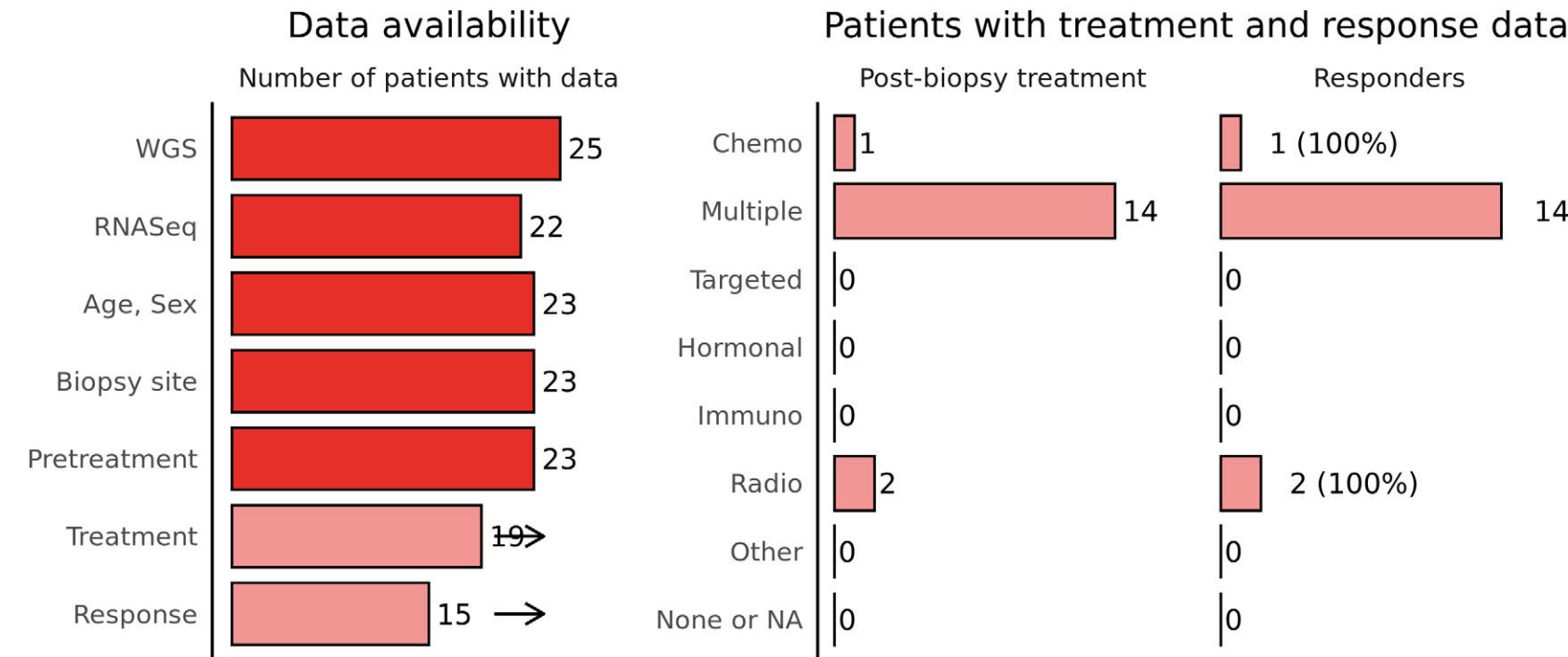Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

**Acronym:**
DOIDs included: 3908, 1324, 5409, 169, 3910, 3907, 5410, 50872, 3905
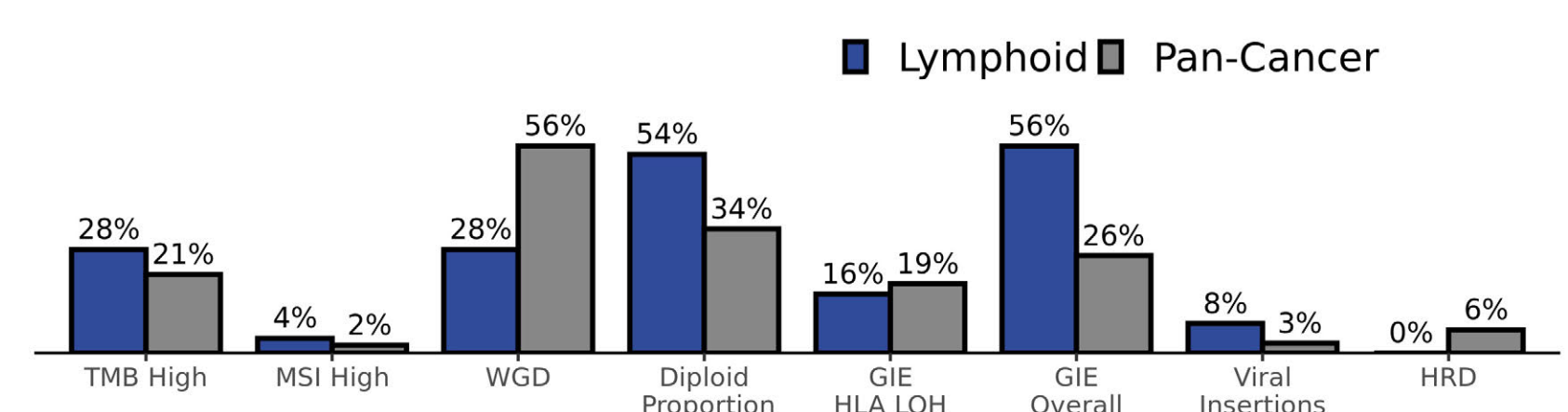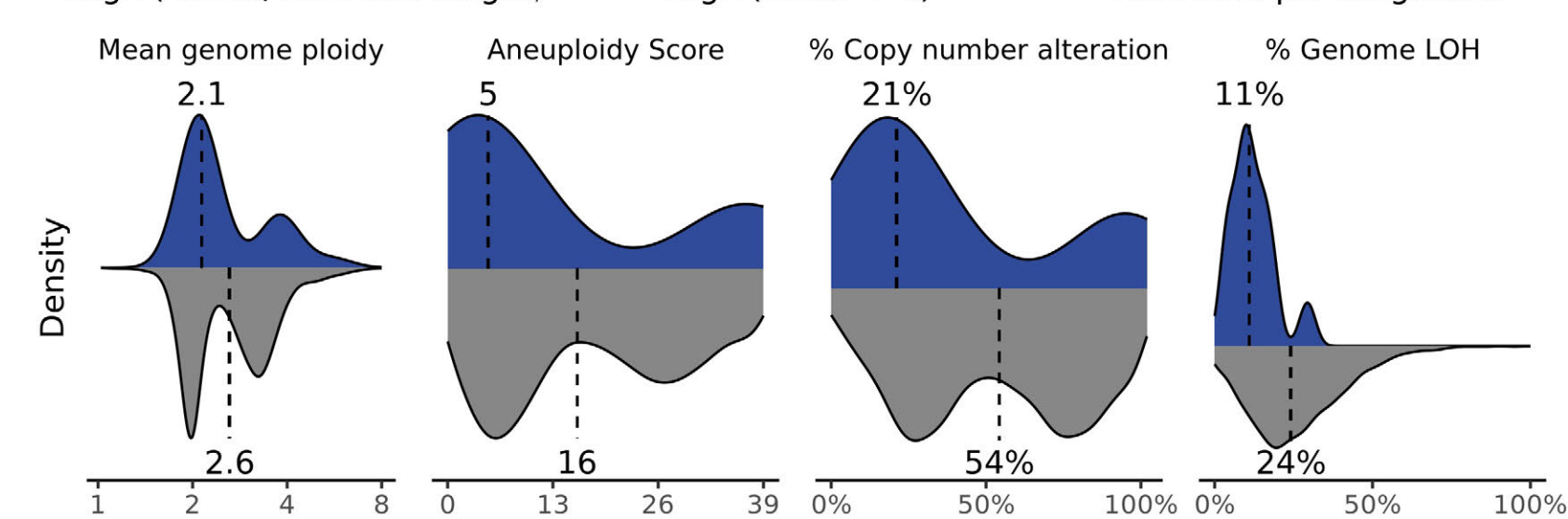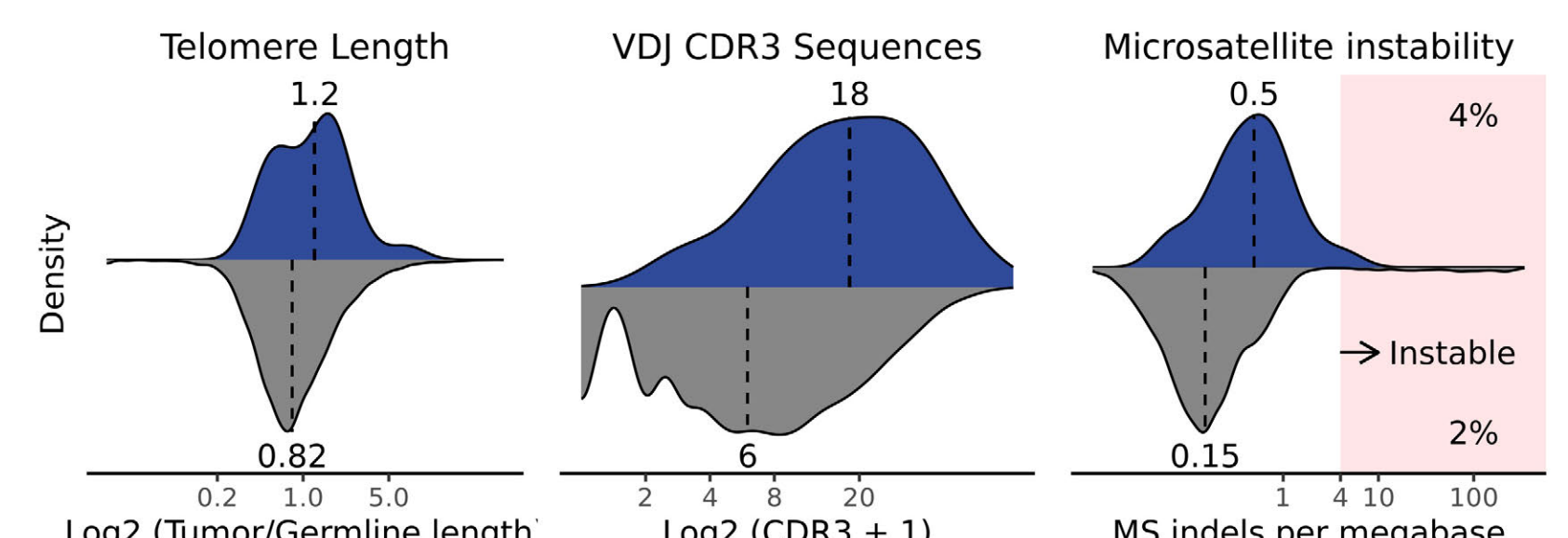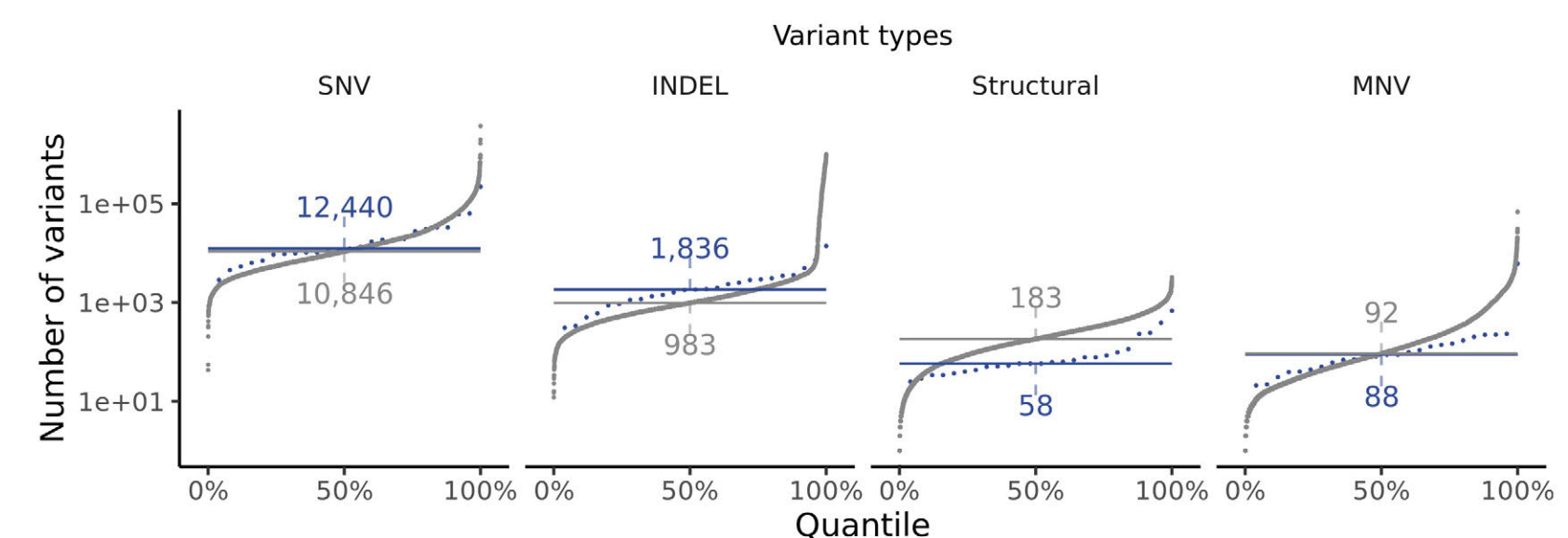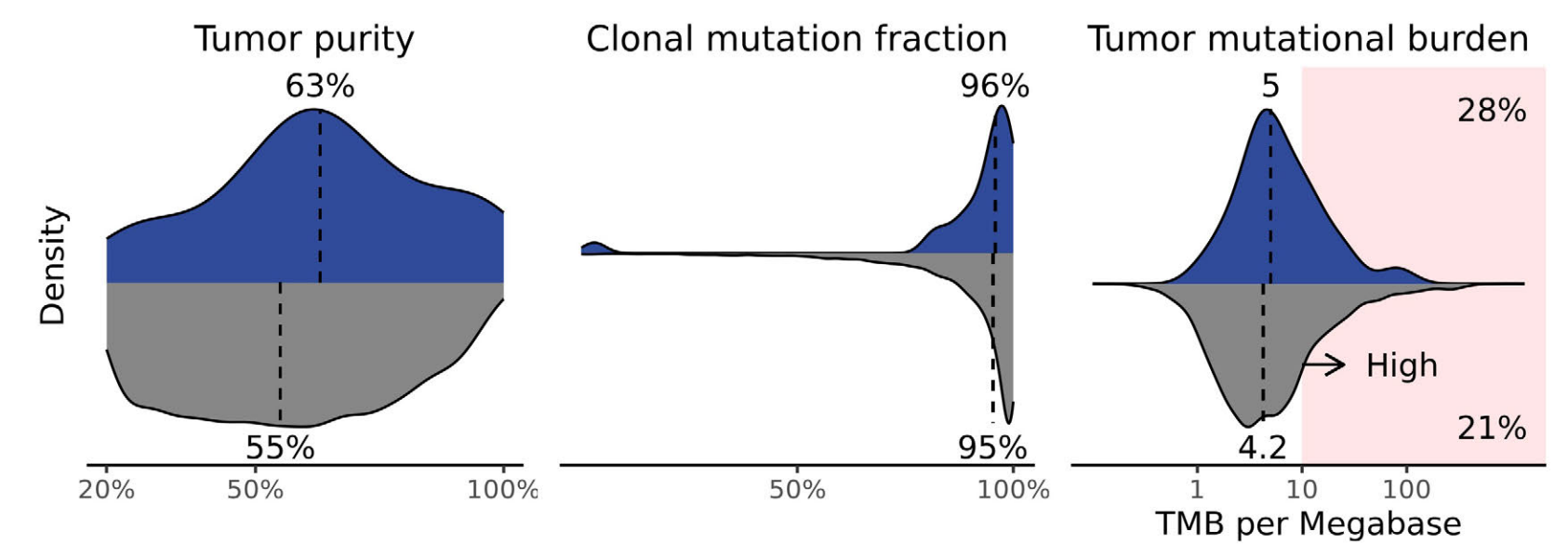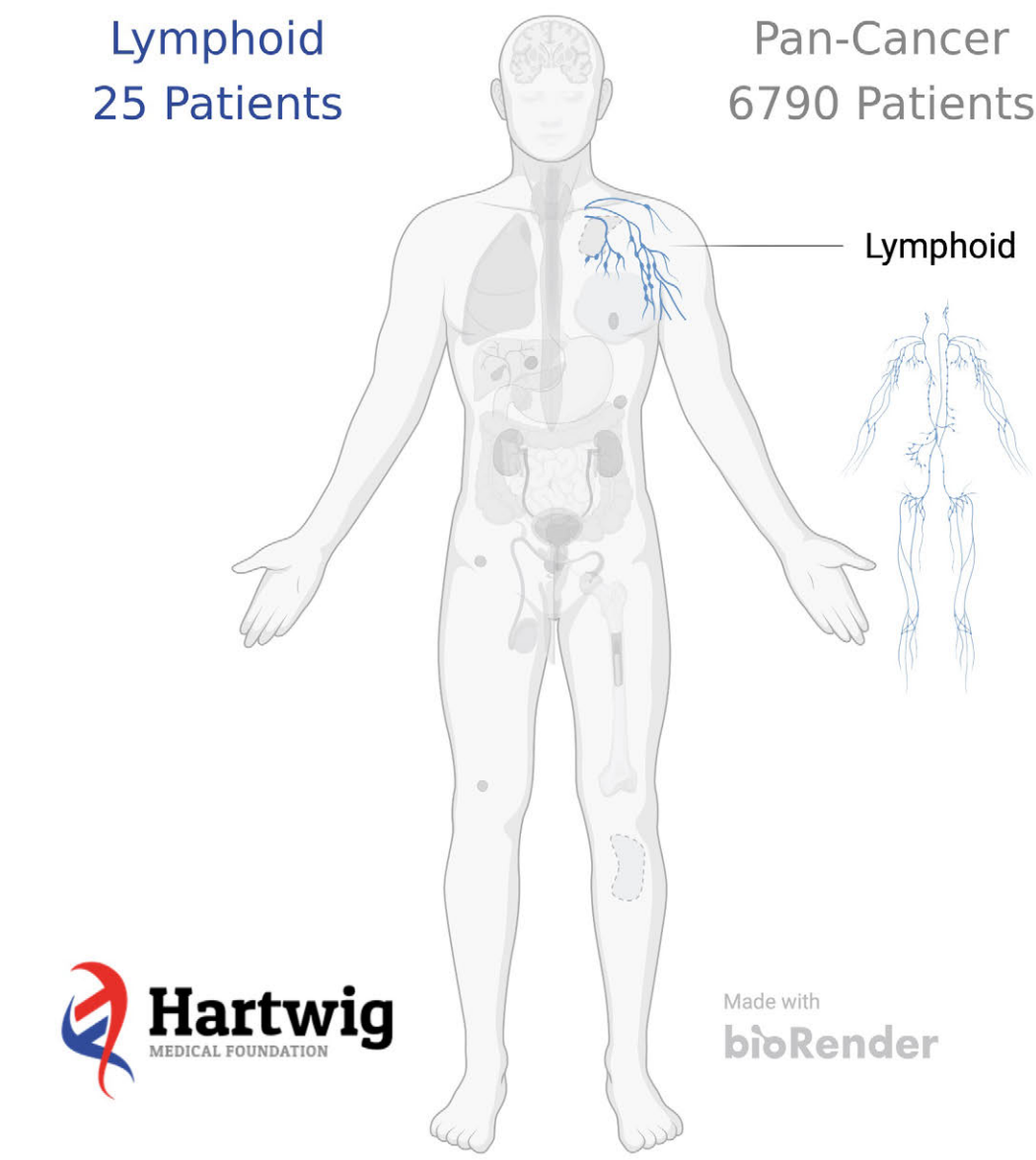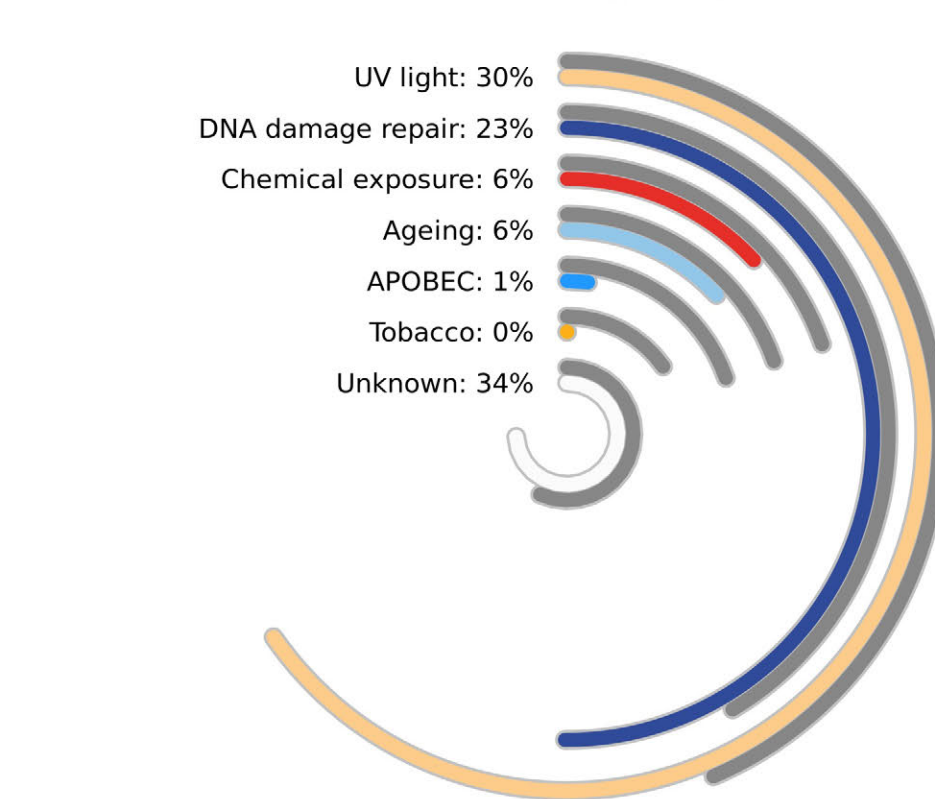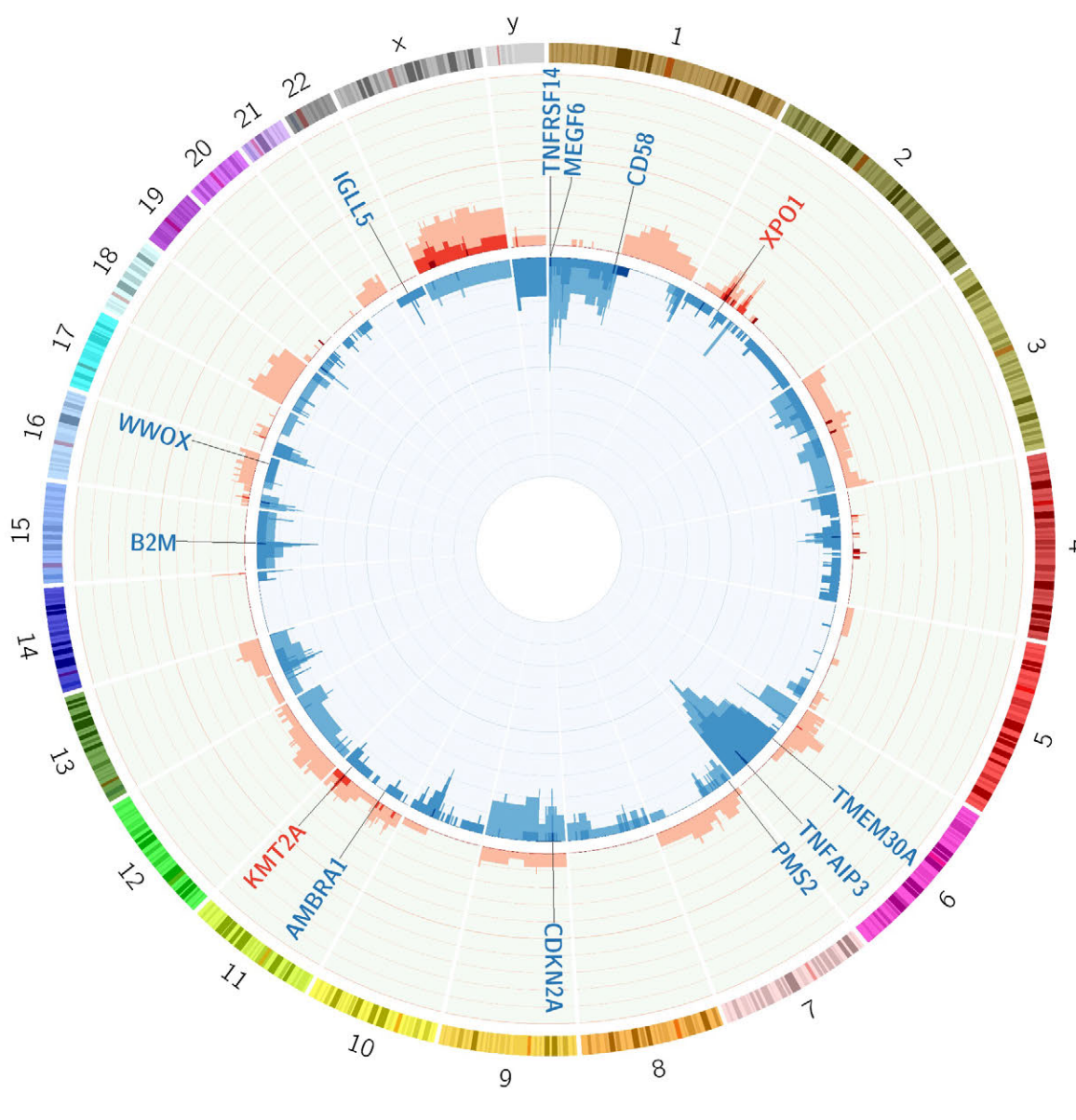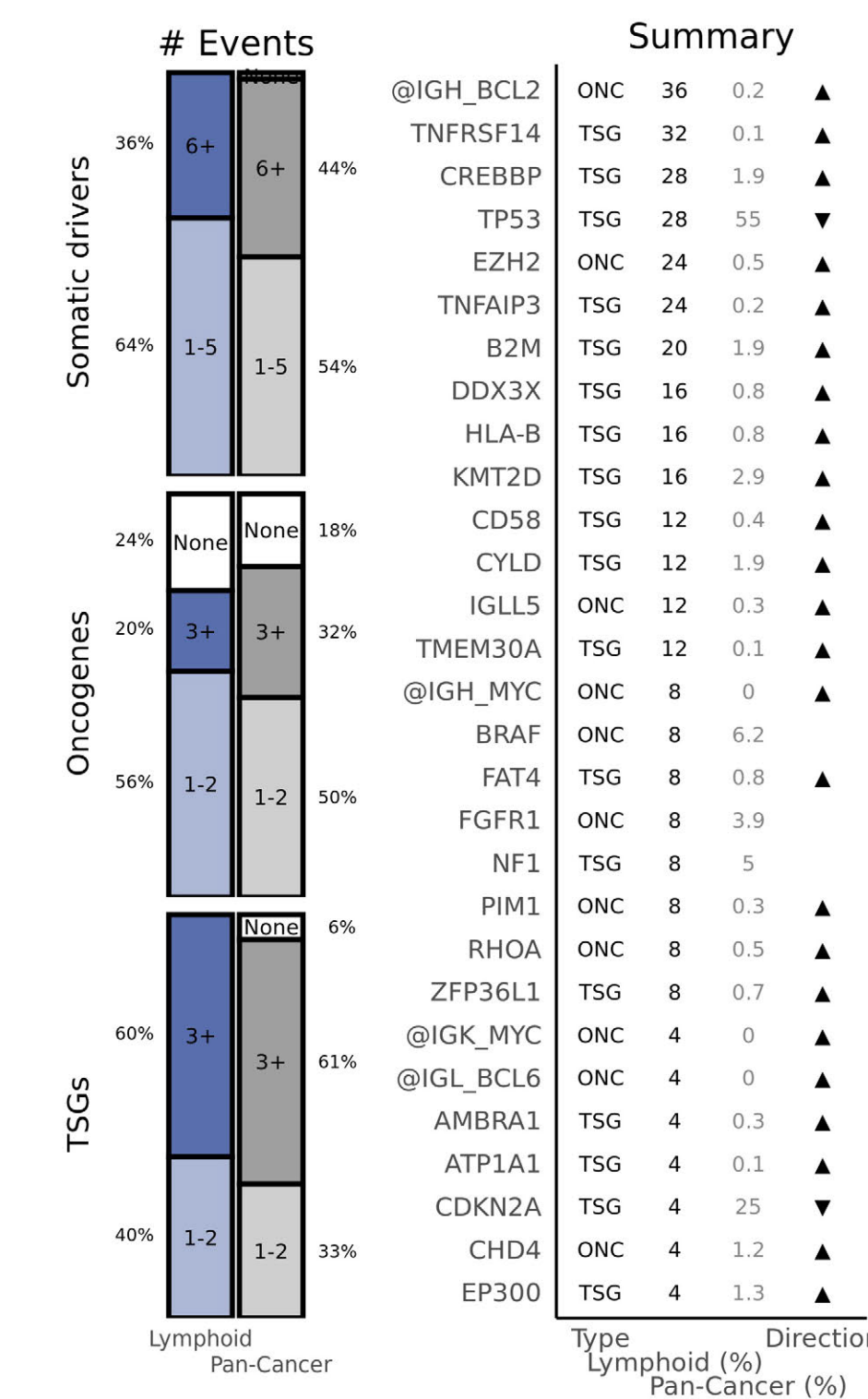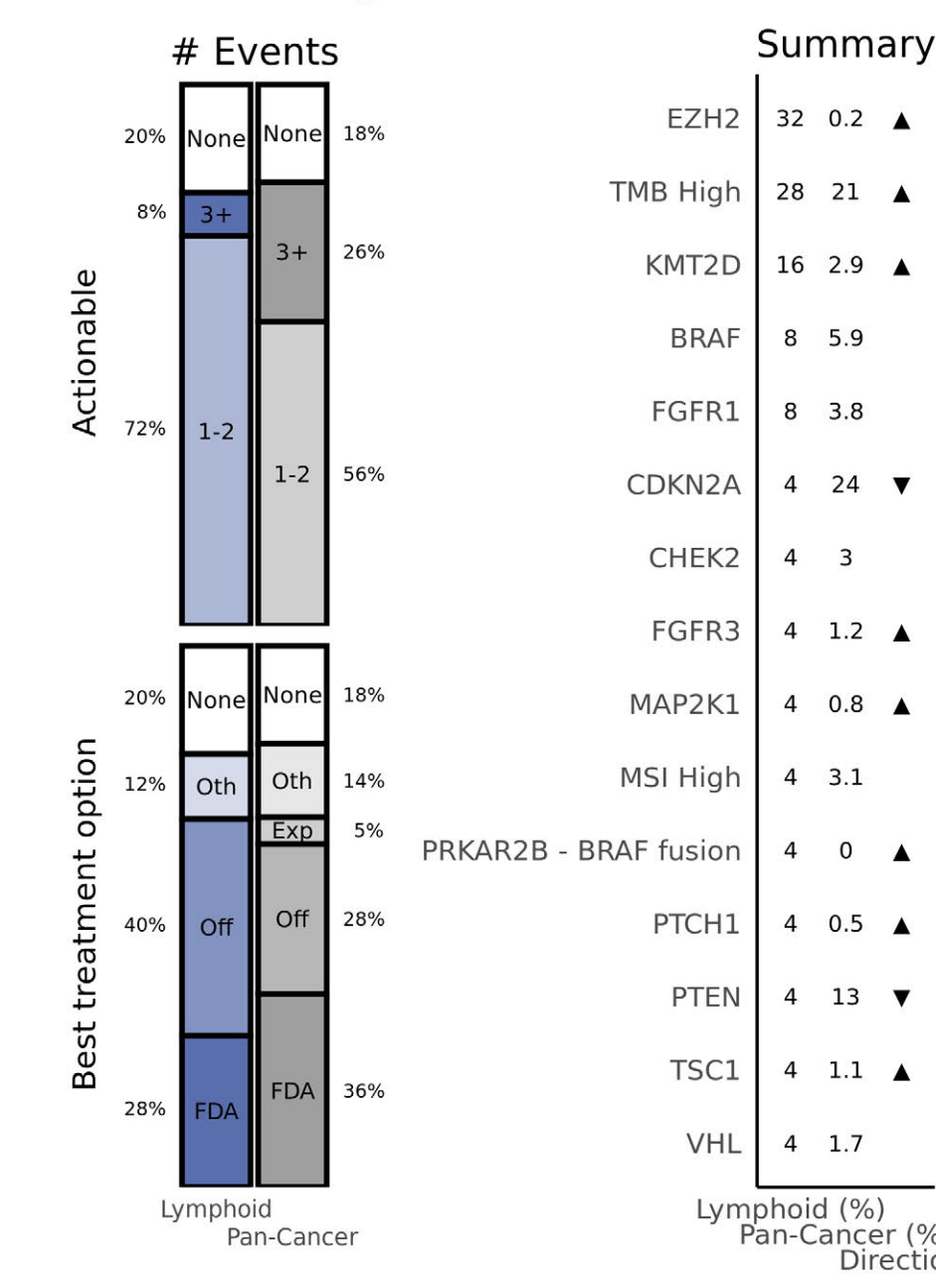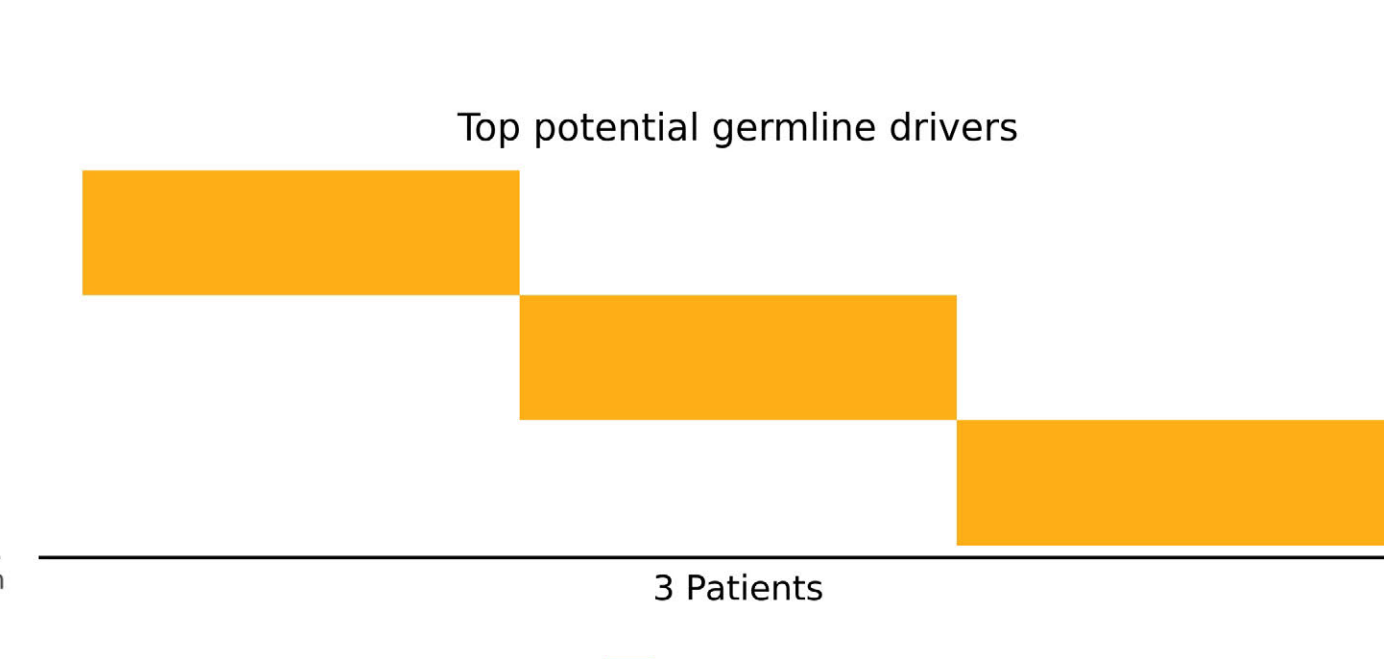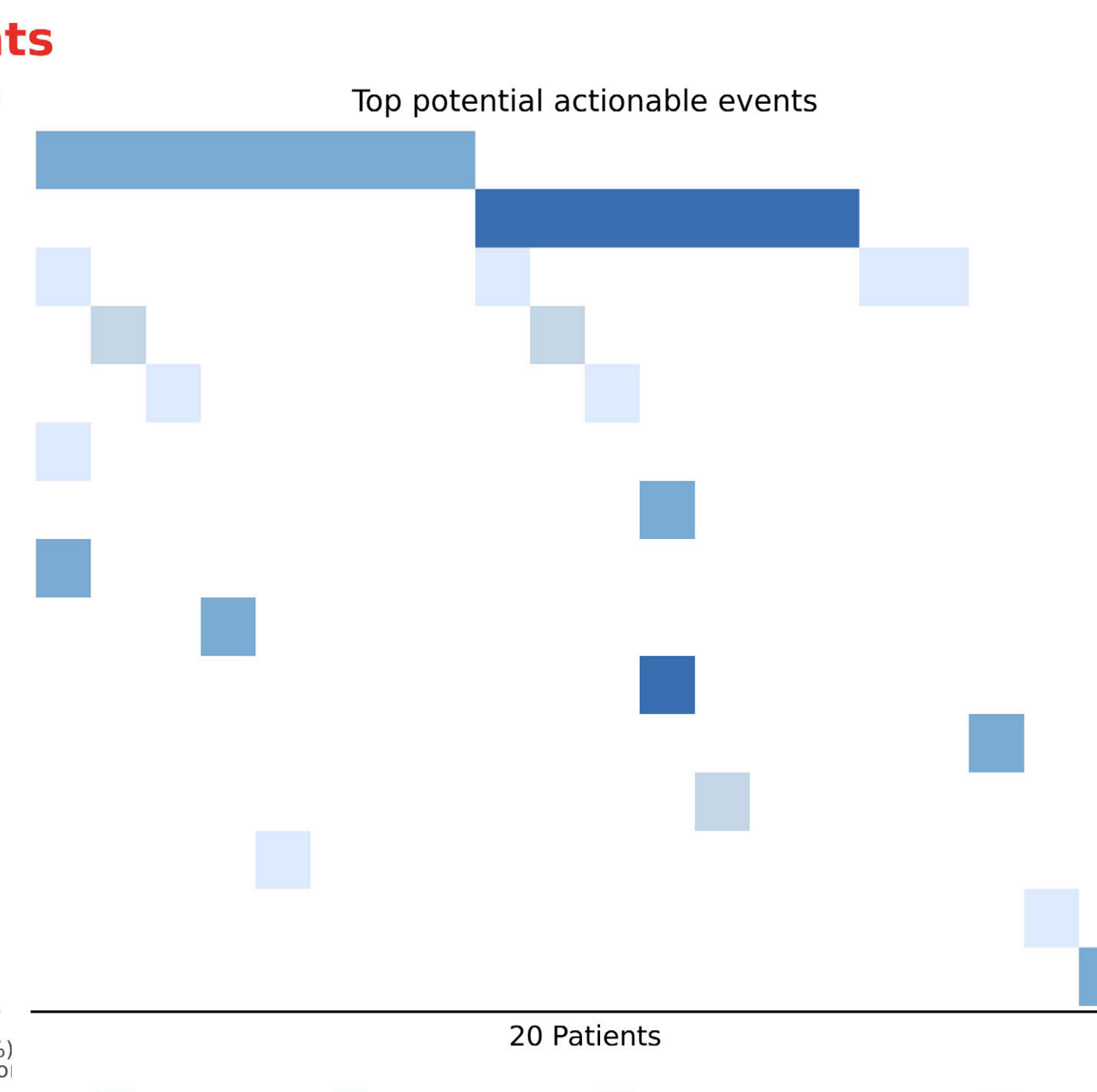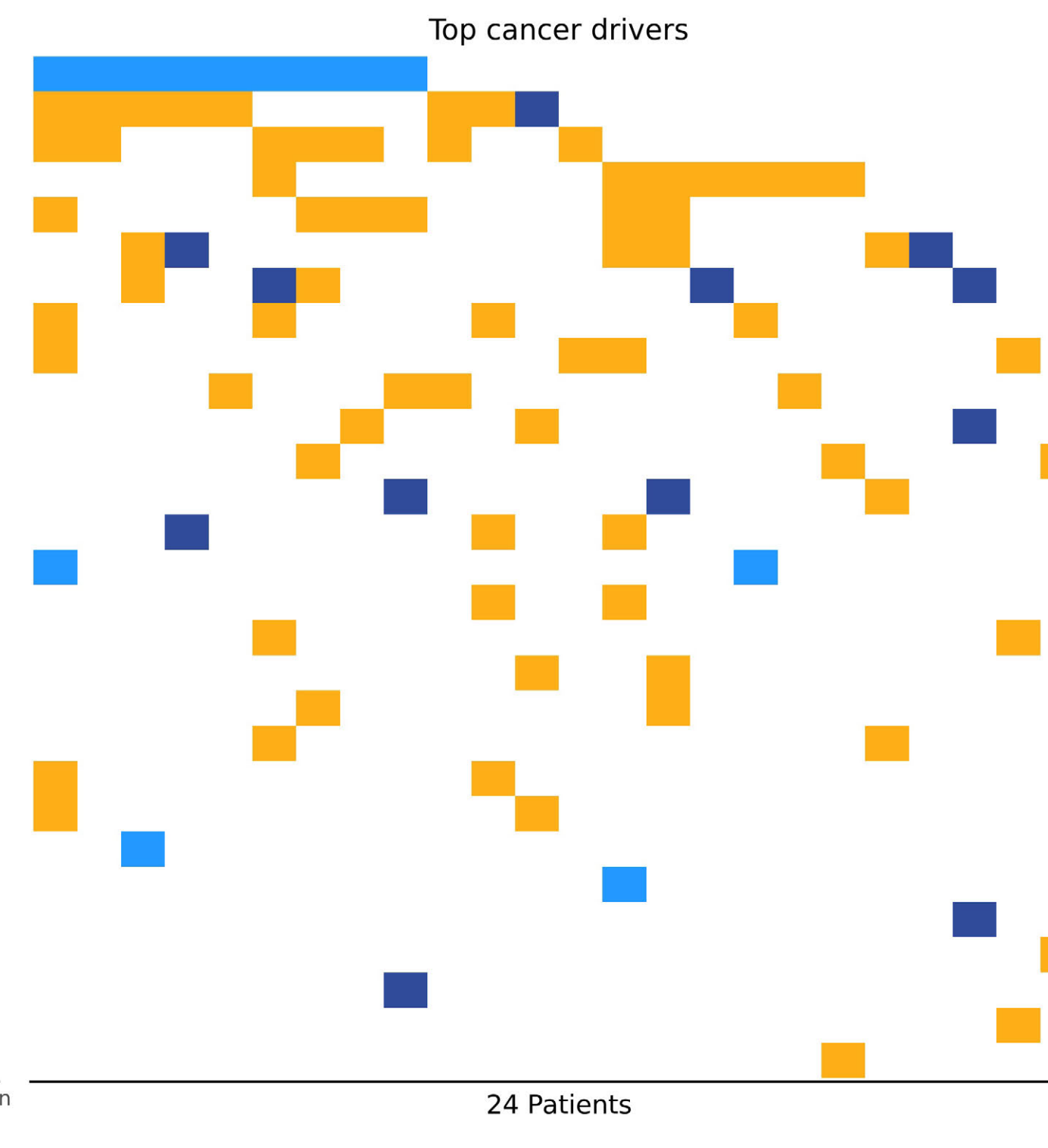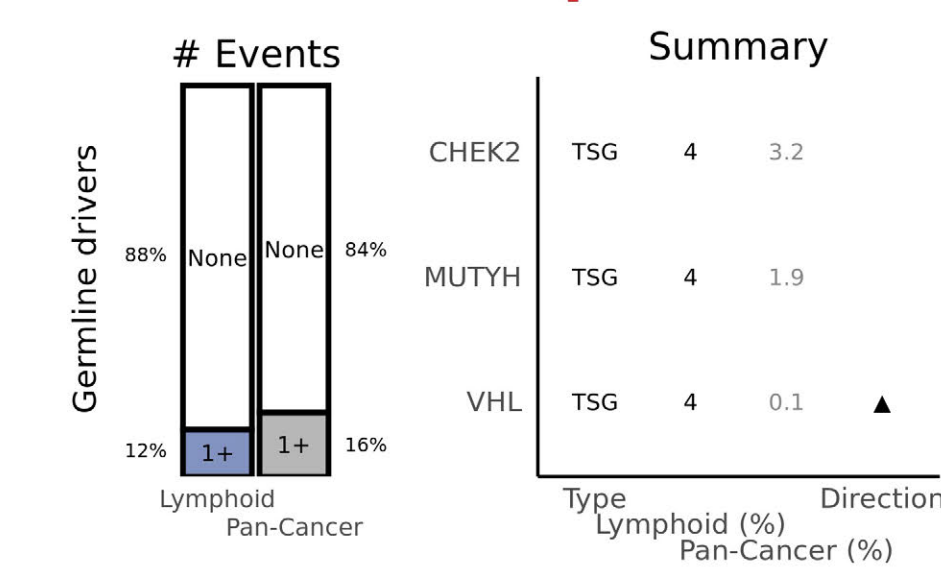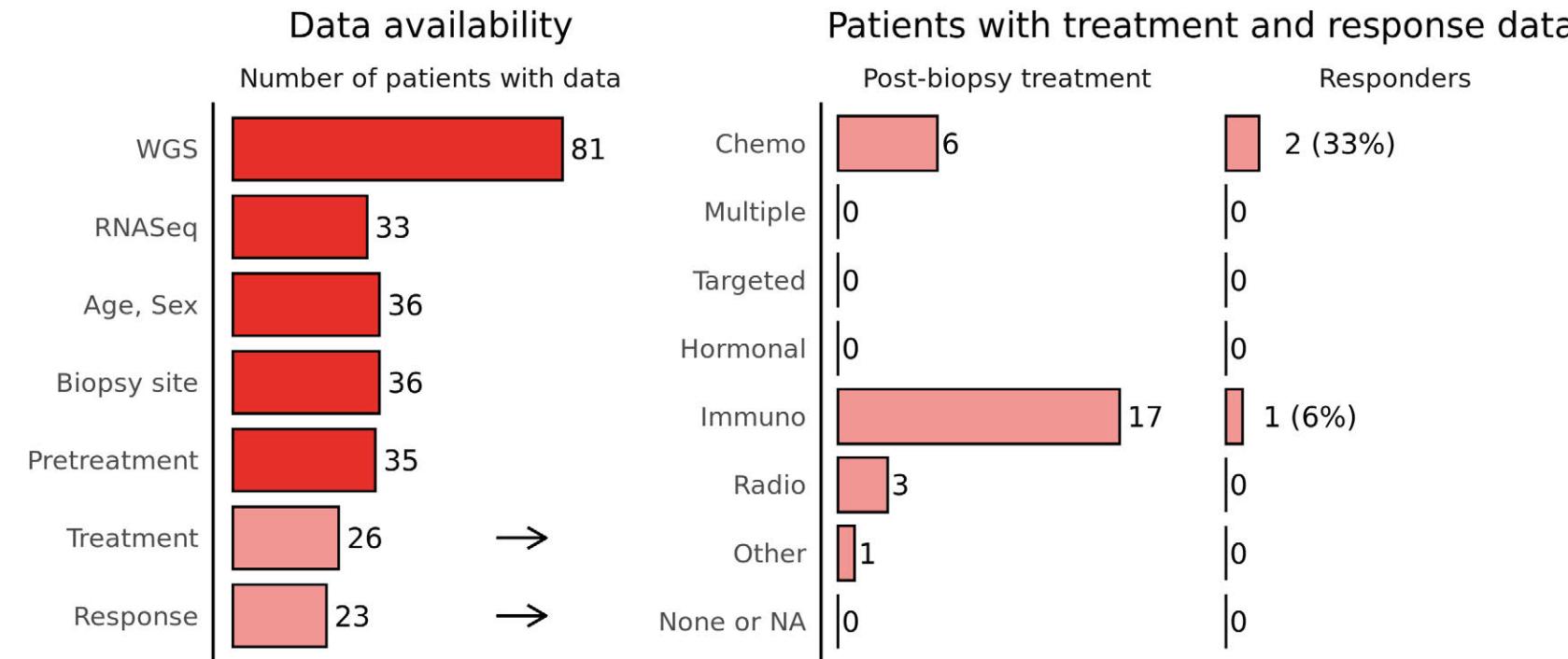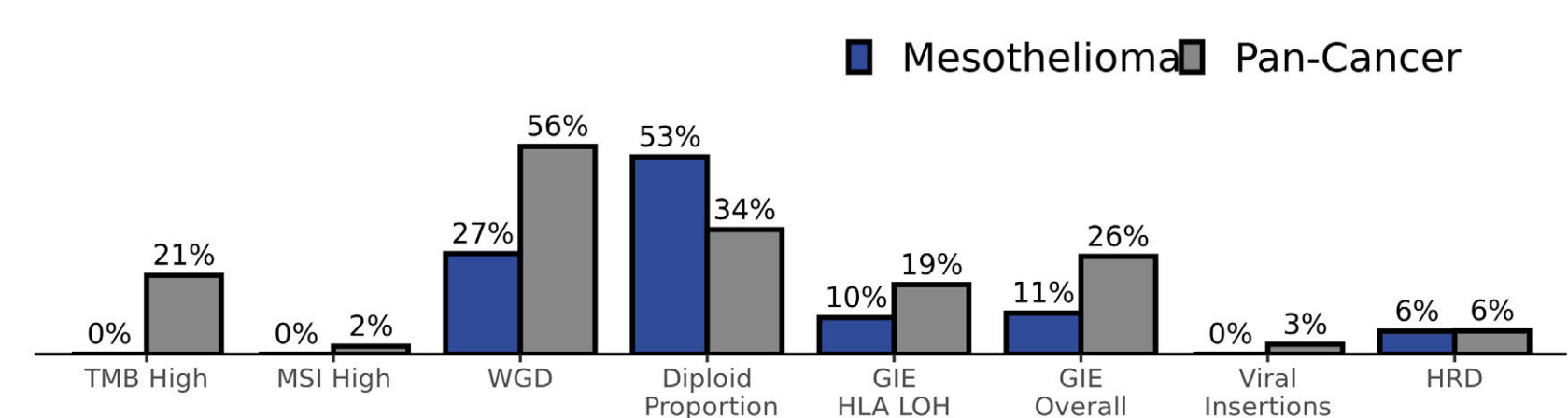Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Other events: Fusions, HMZ (homozygous) Distruptions, Viral insertions, HLA type assumed not captured by panels.
** See documentation for further details on the WGS vs Panel coverage study.
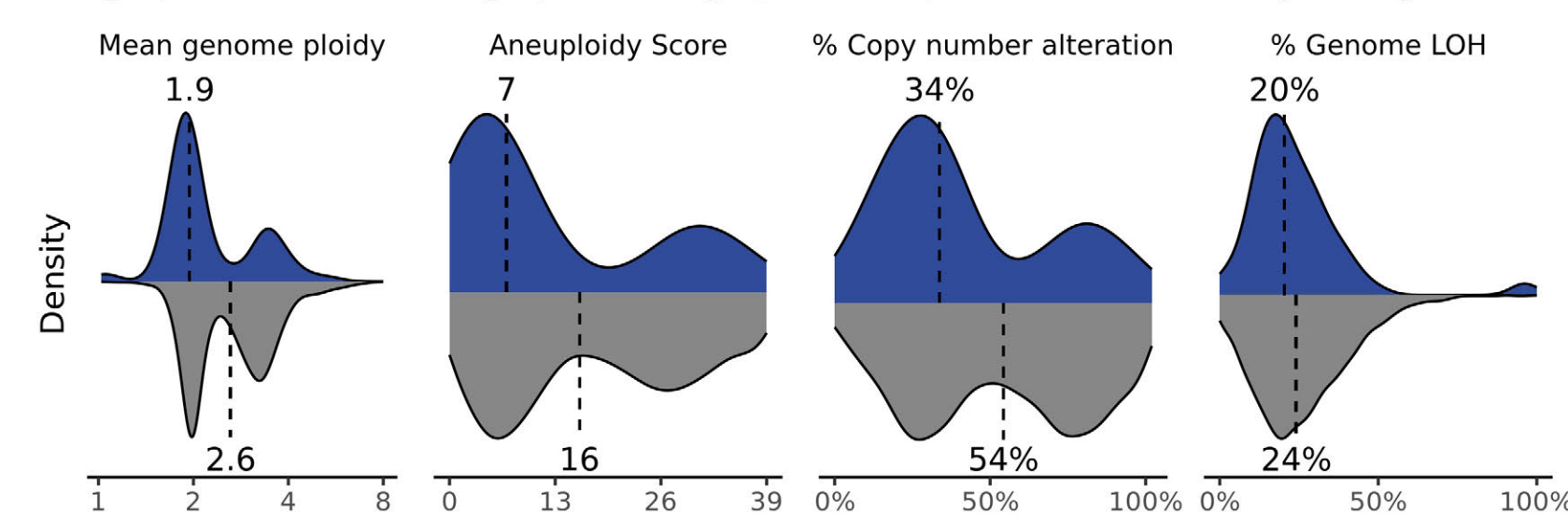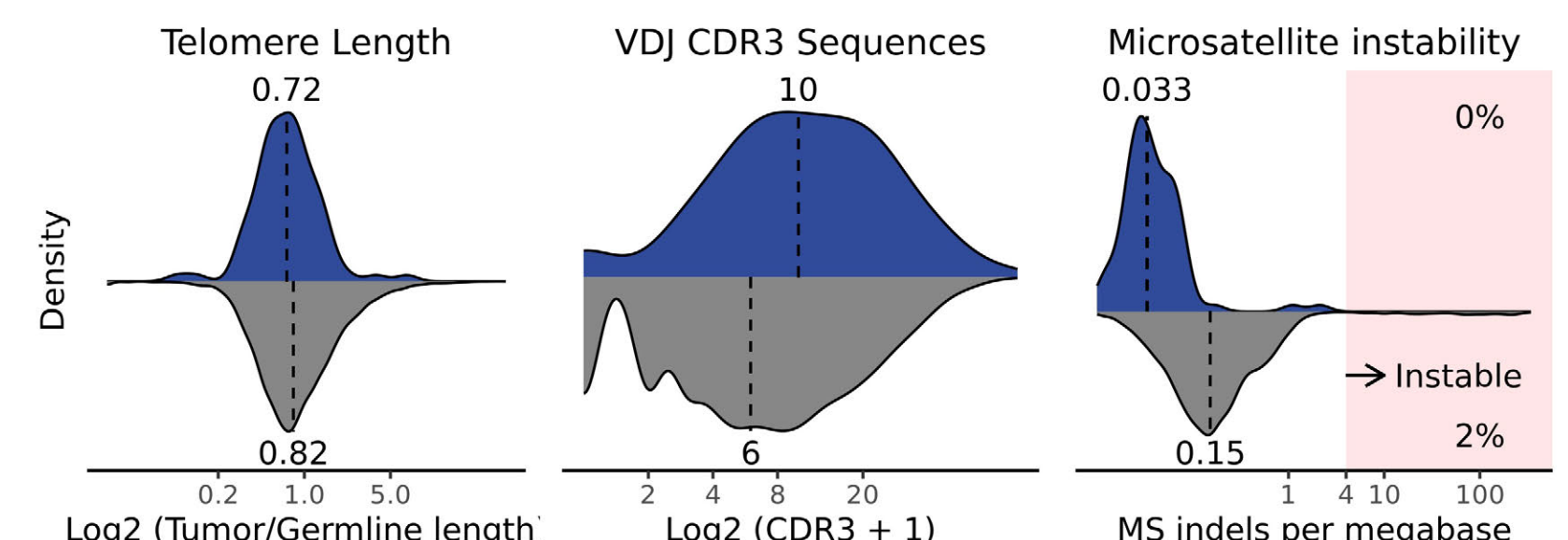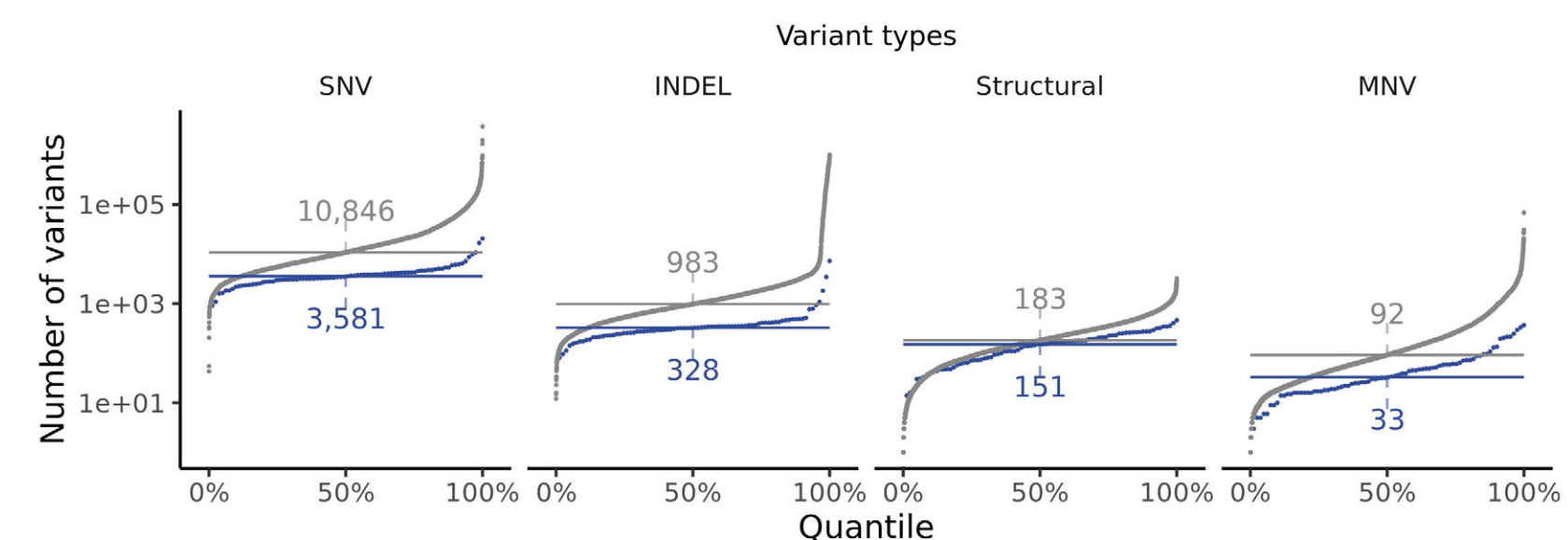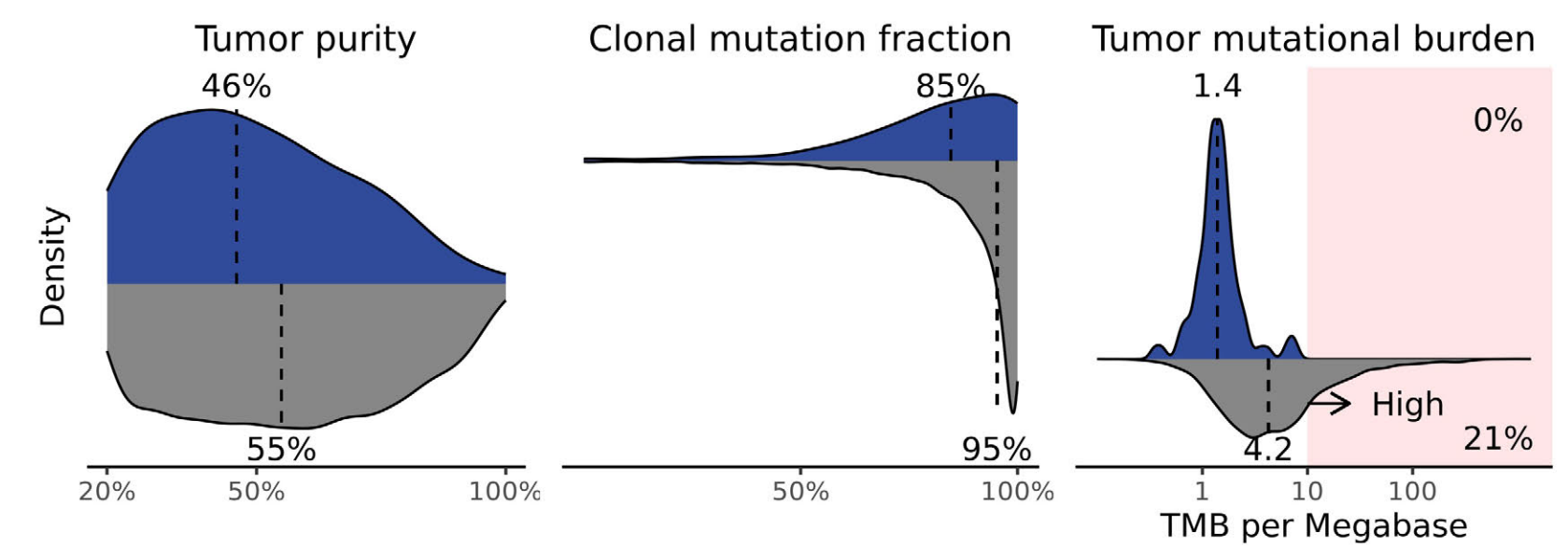
# The Genomic And Actionability Landscape Of B-Cell Non-Hodgkin's Lymphoma

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability

**Number of patients with data**

| Category | Value |
|---|---|
| WGS | 25 |
| RNASeq | 22 |
| Age, Sex | 23 |
| Biopsy site | 23 |
| Pretreatment | 23 |
| Treatment | 19 |
| Response | 15 |

### Patients with treatment and response data

**Post-biopsy treatment / Responders**

| Treatment | Post-biopsy | Responders |
|---|---|---|
| Chemo | 1 | 1 (100%) |
| Multiple | 14 | 14 |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 2 | 2 (100%) |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Lymphoid / Pan-Cancer

| Metric | Lymphoid | Pan-Cancer |
|---|---|---|
| TMB High | 28% | 21% |
| MSI High | 4% | 2% |
| WGD | 28% | 56% |
| Diploid Proportion | 54% | 34% |
| GIE HLA LOH | 16% | 19% |
| GIE Overall | 56% | 26% |
| Viral Insertions | 8% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
63% / 55%

### Clonal mutation fraction
96% / 95%

### Tumor mutational burden
5 — 28% High
4.2 — 21%
TMB per Megabase

### Variant types

| Type | Lymphoid | Pan-Cancer |
|---|---|---|
| SNV | 12,440 | 10,846 |
| INDEL | 1,836 | 983 |
| Structural | 183 | 58 |
| MNV | 92 | 88 |

Number of variants vs Quantile

### Telomere Length
1.2 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
18 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.5 / 0.15 — Instable 4% / 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
16

### % Copy number alteration
21% / 54%

### % Genome LOH
11% / 24%

## Processes Underlying Mutations

| Process | % |
|---|---|
| UV light | 30% |
| DNA damage repair | 23% |
| Chemical exposure | 6% |
| Ageing | 6% |
| APOBEC | 1% |
| Tobacco | 0% |
| Unknown | 34% |

Lymphoid — 25 Patients
Pan-Cancer — 6790 Patients
Lymphoid

Made with bioRender

## Copy Number Alteration Profile

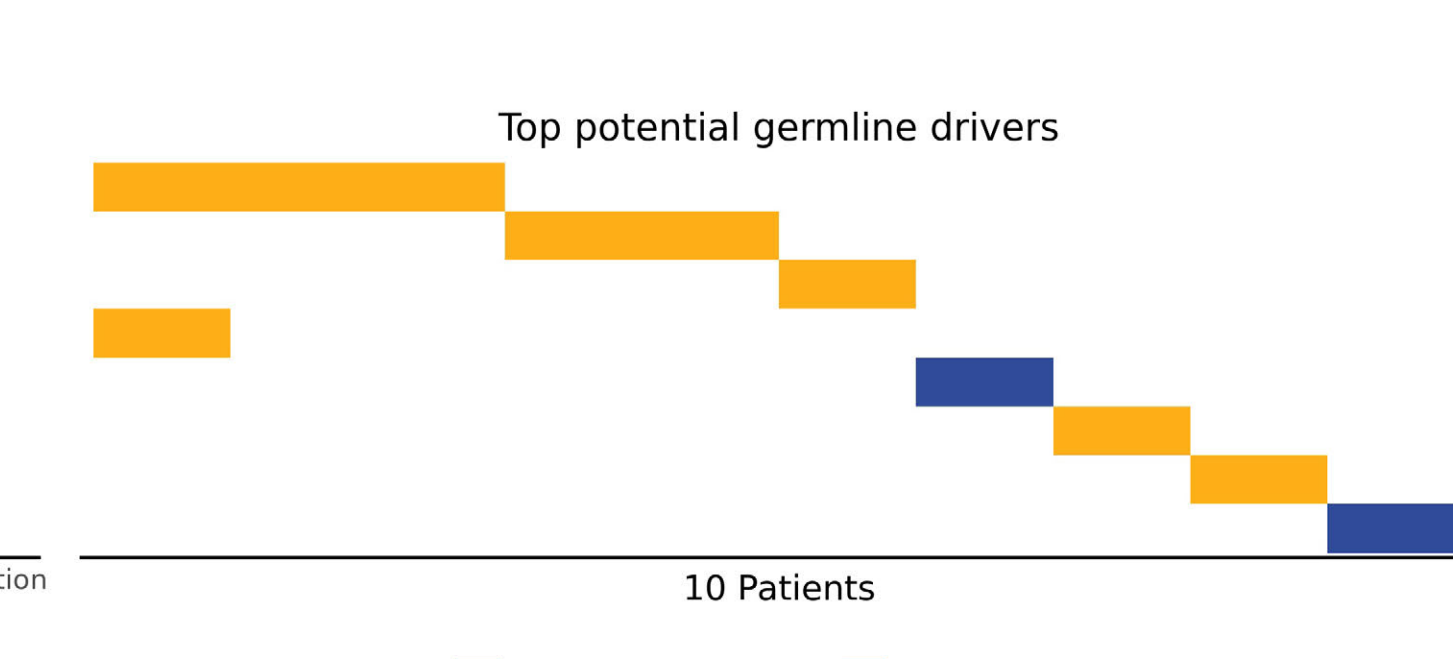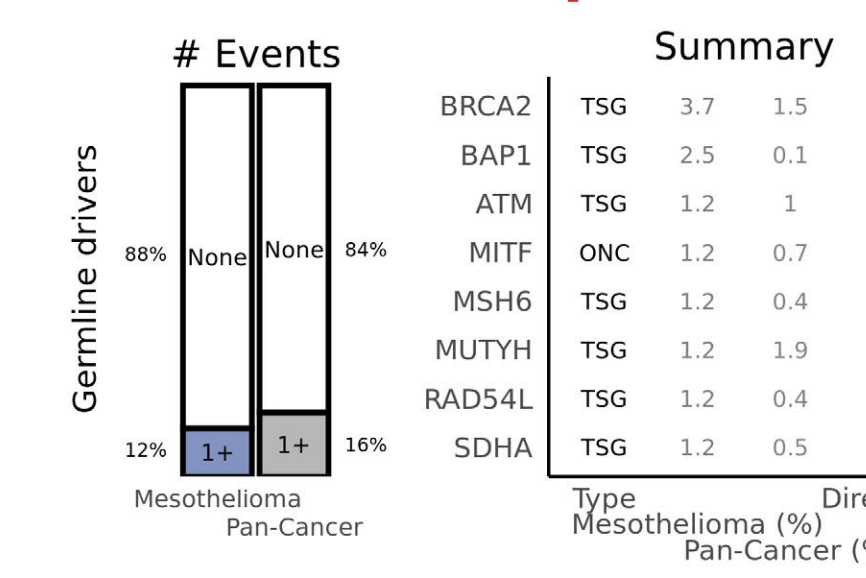

Genes labeled: TNFRSF14, MEGF6, CD58, XPO1, IGLL5, WWOX, B2M, KMT2A, AMBRA1, CDKN2A, TMEM30A, TNFAIP3, PMS2

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers:** 36% / 44% (6+), 64% / 54% (1-5)
**Oncogenes:** 24% / 18% (None), 20% / 32% (3+), 56% / 50% (1-2)
**TSGs:** 60% / 61% (3+), 40% / 33% (1-2)

Lymphoid / Pan-Cancer

| Gene | Type | # | Lymphoid % | Pan-Cancer % | Direction |
|---|---|---|---|---|---|
| @IGH_BCL2 | ONC | 36 | 0.2 | | ▲ |
| TNFRSF14 | TSG | 32 | 0.1 | | ▲ |
| CREBBP | TSG | 28 | 1.9 | | ▲ |
| TP53 | TSG | 28 | 55 | | ▼ |
| EZH2 | ONC | 24 | 0.5 | | ▲ |
| TNFAIP3 | TSG | 24 | 0.2 | | ▲ |
| B2M | TSG | 20 | 1.9 | | ▲ |
| DDX3X | TSG | 16 | 0.8 | | ▲ |
| HLA-B | TSG | 16 | 0.8 | | ▲ |
| KMT2D | TSG | 16 | 2.9 | | ▲ |
| CD58 | TSG | 12 | 0.4 | | ▲ |
| CYLD | TSG | 12 | 1.9 | | ▲ |
| IGLL5 | TSG | 12 | 0.3 | | ▲ |
| TMEM30A | TSG | 12 | 0.1 | | ▲ |
| @IGH_MYC | ONC | 8 | 0 | | |
| BRAF | ONC | 8 | 6.2 | | |
| FAT4 | TSG | 8 | 0.8 | | ▲ |
| FGFR1 | ONC | 8 | 3.9 | | |
| NF1 | TSG | 8 | 5 | | |
| PIM1 | ONC | 8 | 0.3 | | ▲ |
| RHOA | ONC | 8 | 0.5 | | ▲ |
| ZFP36L1 | TSG | 8 | 0.7 | | ▲ |
| @IGK_MYC | ONC | 4 | 0 | | |
| @IGL_BCL6 | ONC | 4 | 0 | | |
| AMBRA1 | TSG | 4 | 0.3 | | ▲ |
| ATP1A1 | TSG | 4 | 0.1 | | ▲ |
| CDKN2A | ONC | 4 | 25 | | ▼ |
| CHD4 | ONC | 4 | 1.2 | | ▲ |
| EP300 | TSG | 4 | 1.3 | | ▲ |

Type / Direction — Lymphoid (%) / Pan-Cancer (%)

**Top cancer drivers** — 24 Patients

Legend: DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events / Summary

**Actionable:** 20% / 18% (None), 8% / 26% (3+), 72% / 56% (1-2)
**Best treatment option:** 20% / 18% (None), 12% / 14% (Oth), 0% / (Exp), 40% / 28% (Off), 28% / 36% (FDA)

Lymphoid / Pan-Cancer

| Gene | # | Lymphoid % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| EZH2 | 32 | 0.2 | | ▲ |
| TMB High | 28 | 21 | | ▲ |
| KMT2D | 16 | 2.9 | | ▲ |
| BRAF | 8 | 5.9 | | |
| FGFR1 | 8 | 3.8 | | |
| CDKN2A | 4 | 24 | | ▼ |
| CHEK2 | 4 | 3 | | |
| FGFR3 | 4 | 1.2 | | ▲ |
| MAP2K1 | 4 | 0.8 | | ▲ |
| MSI High | 4 | 3.1 | | |
| PRKAR2B - BRAF fusion | 4 | 0 | | ▲ |
| PTCH1 | 4 | 0.5 | | ▲ |
| PTEN | 4 | 13 | | ▼ |
| TSC1 | 4 | 1.1 | | ▲ |
| VHL | 4 | 1.7 | | |

Lymphoid (%) / Pan-Cancer (%) / Direction

**Top potential actionable events** — 20 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events / Summary

**Germline drivers:** 88% / 84% (None), 12% / 16% (1+)

Lymphoid / Pan-Cancer

| Gene | Type | # | Value | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 4 | 3.2 | |
| MUTYH | TSG | 4 | 1.9 | |
| VHL | TSG | 4 | 0.1 | ▲ |

Type — Lymphoid (%) / Pan-Cancer (%) — Direction

**Top potential germline drivers** — 3 Patients

Legend: SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Experimental/Other | None |
|---|---|---|---|---|
| WGS | 7 | 10 | 4 | 4 |
| Comprehensive 521 gene panel | 7 | 9 | 3 | 6 |
| Targeted 50 gene panel | 1 | 7 | 1 | 16 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | FDA | Drug Rep | Exp/Other | Total |
|---|---|---|---|---|
| WGS | 0.32 | 0.52 | 0.6 | 1.6 |
| Comprehensive 521 gene panel | 0.32 | 0.48 | 0.52 | 1.4 |
| Targeted 50 gene panel | 0.28 | | | 0.4 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

| Category | Event | Missed |
|---|---|---|
| Drug Repurposing | Fusion | 1 |
| Experimental/Other Guidelines | Partial CN Loss | 1 |
| Other | Partial CN Loss | 2 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

| Category | Event | Missed |
|---|---|---|
| FDA Approved | TMB High | 7 |
| Drug Repurposing | Small Variant | 5 |
| Drug Repurposing | Fusion | 1 |
| Experimental/Other Guidelines | Partial CN Loss | 1 |
| Experimental/Other Guidelines | Splice Site | 1 |
| Other | Small Variant | 10 |
| Other | Partial CN Loss | 2 |
| Other | Full CN Loss | 1 |
| Other | Splice Site | 1 |

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Mesothelioma

Website: https://www.hartwigmedicalfoundation.nl
Tools: https://github.com/hartwigmedical/hmftools
Database: https://www.hartwigmedicalfoundation.nl/en/data/database/

## Cohort Metadata

### Data availability
Number of patients with data

- WGS: 81
- RNASeq: 33
- Age, Sex: 36
- Biopsy site: 36
- Pretreatment: 35
- Treatment: 26 →
- Response: 23 →

### Patients with treatment and response data

Post-biopsy treatment / Responders

- Chemo: 6 / 2 (33%)
- Multiple: 0 / 0
- Targeted: 0 / 0
- Hormonal: 0 / 0
- Immuno: 17 / 1 (6%)
- Radio: 3 / 0
- Other: 1 / 0
- None or NA: 0 / 0

## Processes Underlying Mutations

- Chemical exposure: 17%
- DNA damage repair: 16%
- Ageing: 16%
- APOBEC: 6%
- Tobacco: 4%
- UV light: 1%
- Unknown: 40%

## Tumor Characteristics

Mesothelioma / Pan-Cancer

- TMB High: 0% / 21%
- MSI High: 0% / 2%
- WGD: 27% / 56%
- Diploid Proportion: 53% / 34%
- GIE HLA LOH: 10% / 19%
- GIE Overall: 11% / 26%
- Viral Insertions: 0% / 3%
- HRD: 6% / 6%

## Mutational Landscape

### Tumor purity
46% / 55%

### Clonal mutation fraction
85% / 95%

### Tumor mutational burden
1.4 / 4.2 / High 21% / 0%
TMB per Megabase

### Variant types

- SNV: 10,846 / 3,581
- INDEL: 983 / 328
- Structural: 183 / 151
- MNV: 92 / 33

Number of variants / Quantile

### Telomere Length
0.72 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
10 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.033 / 0.15 / Instable 2% / 0%
MS indels per megabase

### Mean genome ploidy
1.9 / 2.6

### Aneuploidy Score
7 / 16

### % Copy number alteration
34% / 54%

### % Genome LOH
20% / 24%

## Mesothelioma 81 Patients / Pan-Cancer 6790 Patients

## Copy Number Alteration Profile

Genes labeled around circos plot: HIC13, NTRK1, SETD2, BAP1, PBRM1, CCSER1, LMBRD2, CCND3, PRKN, SGC2, CDKN2A, FANCC, PTCH1, LATS2, ARID2, RAD51B, PRKACA, CALR, CD78B, BAP1, USP8, PPM1D, NF2, DEPDC5, DMD, KDM6A, DIAPH2

## Cancer Driver Landscape

### Somatic drivers / Oncogenes / TSGs

# Events and Summary

Genes (Type, Mesothelioma %, Pan-Cancer %, Direction):
- CDKN2A: TSG 64 / 25
- BAP1: TSG 54 / 2.7 ▲
- NF2: TSG 47 / 1.7 ▲
- SETD2: TSG 19 / 2.1 ▲
- TP53: TSG 14 / 55 ▼
- LATS2: TSG 9.9 / 0.4 ▲
- PBRM1: TSG 9.9 / 3.2 ▲
- DDX3X: TSG 7.4 / 0.8 ▲
- TERT: ONC 6.2 / 13 ▼
- CYLD: TSG 4.9 / 1.9
- DMD: TSG 4.9 / 3.5
- KDM6A: TSG 4.9 / 3.7
- ARID2: TSG 3.7 / 1.8
- ATM: TSG 3.7 / 2.9
- MGA: TSG 3.7 / 1.5
- PTCH1: TSG 3.7 / 0.5 ▲
- STK11: TSG 3.7 / 4.1
- TRAF7: TSG 3.7 / 0.3 ▲
- ARHGAP35: TSG 2.5 / 0.6 ▲
- ARID1B: TSG 2.5 / 1.2
- B2M: TSG 2.5 / 1.9
- CALR: ONC 2.5 / 0.4 ▲
- CCSER1: TSG 2.5 / 1.6
- CHD4: ONC 2.5 / 1.2
- DEPDC5: TSG 2.5 / 0.4 ▲
- DIAPH2: TSG 2.5 / 0.8
- DNMT3A: TSG 2.5 / 0.6 ▲
- FANCC: TSG 2.5 / 0.1 ▲
- FBXW7: TSG 2.5 / 2.8

78 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange)

## Potentially Actionable Events

### Top potential actionable events

Genes (Mesothelioma %, Pan-Cancer %, Direction):
- CDKN2A: 64 / 24 ▲
- NF2: 47 / 1.6 ▲
- HR deficiency: 6.2 / 5.8
- ATM: 4.9 / 3.5
- BRCA2: 3.7 / 2.4
- PTCH1: 3.7 / 0.5 ▲
- KMT2D: 2.5 / 2.9
- RAD51B: 2.5 / 0.7 ▲
- TSC1: 2.5 / 1.1
- CHEK2: 1.2 / 3
- EIF2AK2 - ALK fusion: 1.2 / 0 ▲
- ERBB4: 1.2 / 0.5
- MOXD1 - ROS1 fusion: 1.2 / 0 ▲
- MTOR: 1.2 / 0.4 ▲
- RAD51C: 1.2 / 0.1 ▲

62 Patients

Legend: Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### Top potential germline drivers

Genes (Type, Mesothelioma %, Pan-Cancer %, Direction):
- BRCA2: TSG 3.7 / 1.5
- BAP1: TSG 2.5 / 0.1 ▲
- ATM: TSG 1.2 / 1
- MITF: ONC 1.2 / 0.7
- MSH6: TSG 1.2 / 0.4
- MUTYH: TSG 1.2 / 1.9
- RAD54L: TSG 1.2 / 1 ▲
- SDHA: TSG 1.2 / 0.5

10 Patients

Legend: STRUCTURAL_VARIANT (blue), SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy
- WGS: 13 / 6 / 45 / 17
- Comprehensive 521 gene panel: 9 / 4 / 43 / 25
- Targeted 50 gene panel: 43 / 37

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy
- WGS: 0.22 / 1.2 / 1.5
- Comprehensive 521 gene panel: 0.84 / 1
- Targeted 50 gene panel: 0.53 / 0.5

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS
FDA Approved / Drug Repurposing: HRD 5, Fusion, Partial CN Loss 2
Experimental/Other Guidelines: Partial CN Loss 4
Other: Partial CN Loss 22, HMZ Disruption 4, Full CN Loss 2

### Top missed events by Targeted Panel vs WGS
FDA Approved / Drug Repurposing: Small Variant 8, HRD 5, Fusion 2, Partial CN Loss 2
Experimental/Other Guidelines: Partial CN Loss 4
Other: Small Variant 24, Partial CN Loss 22, HMZ Disruption 4, Full CN Loss 2, Splice Site 1

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.

Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.

Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.

Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.

Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.

Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).

Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red); moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).

Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.

Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.

TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: MESO
DOIDs included: 1790, 50686, 7474
Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Other events: Fusions, HMZ (homozygous) Distruptions, Viral inserts, HLA type assumed not captured by panels.
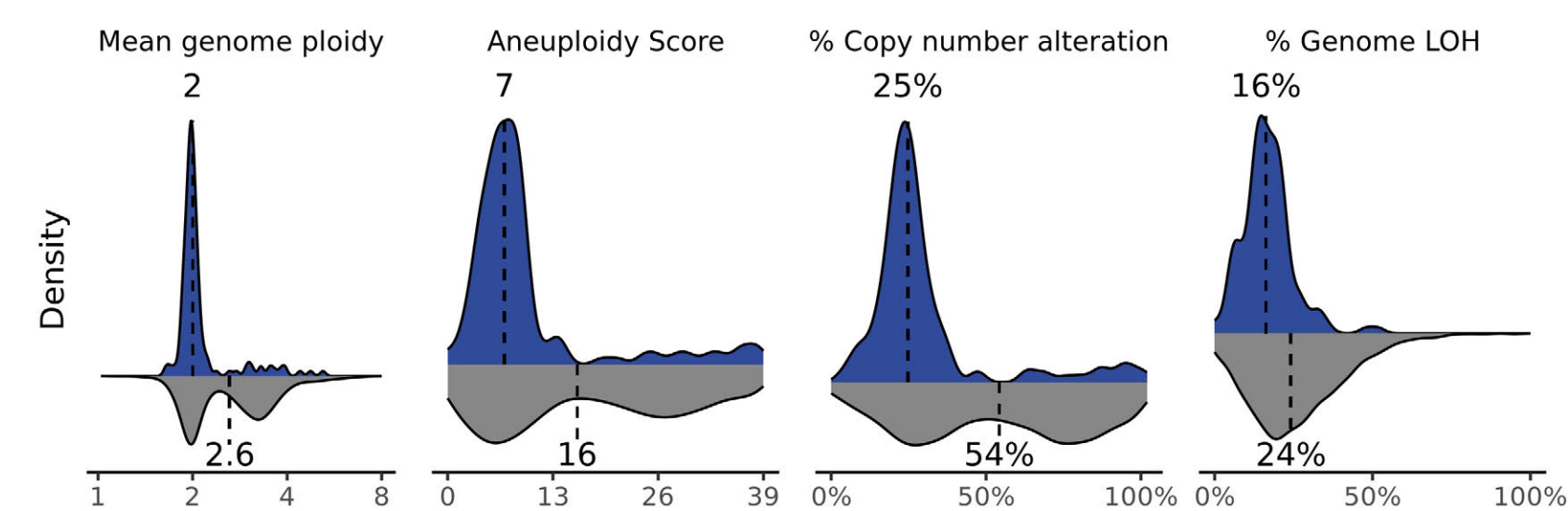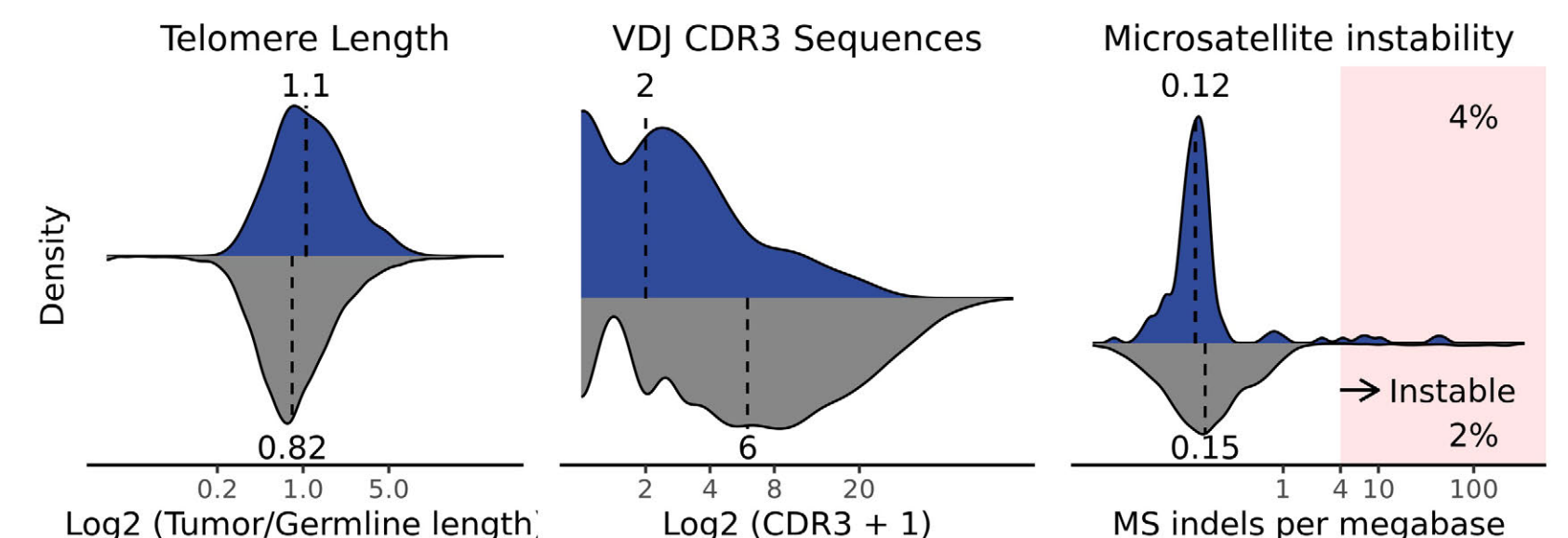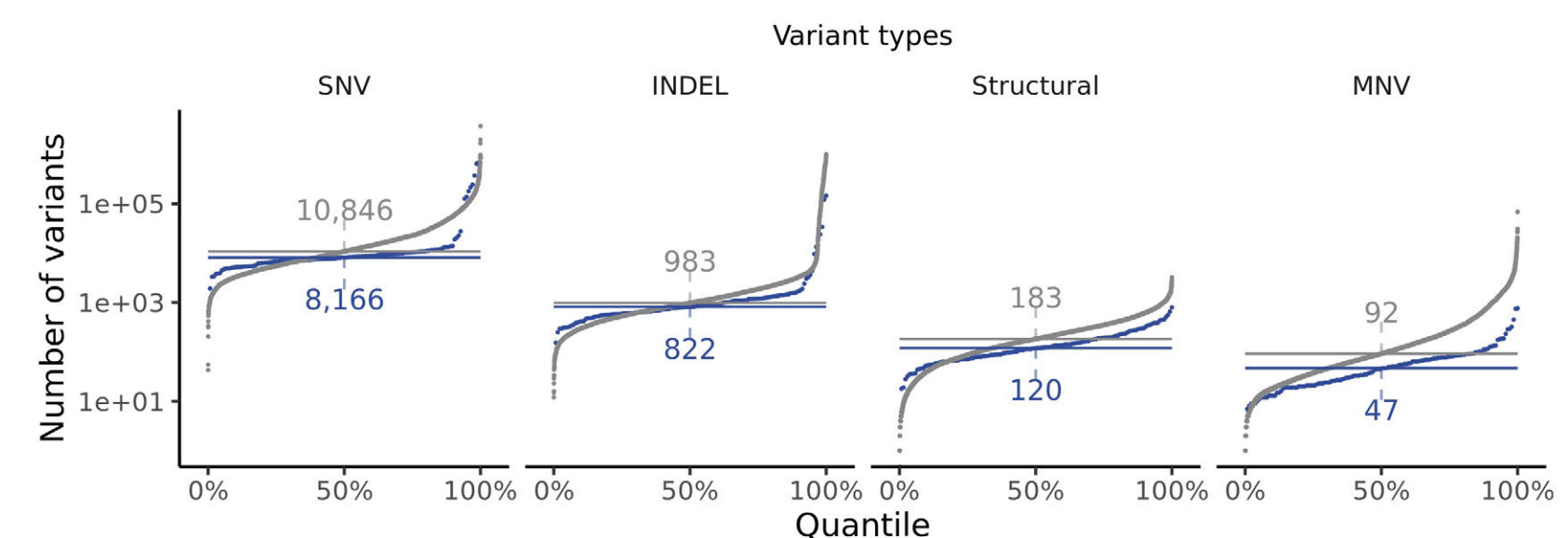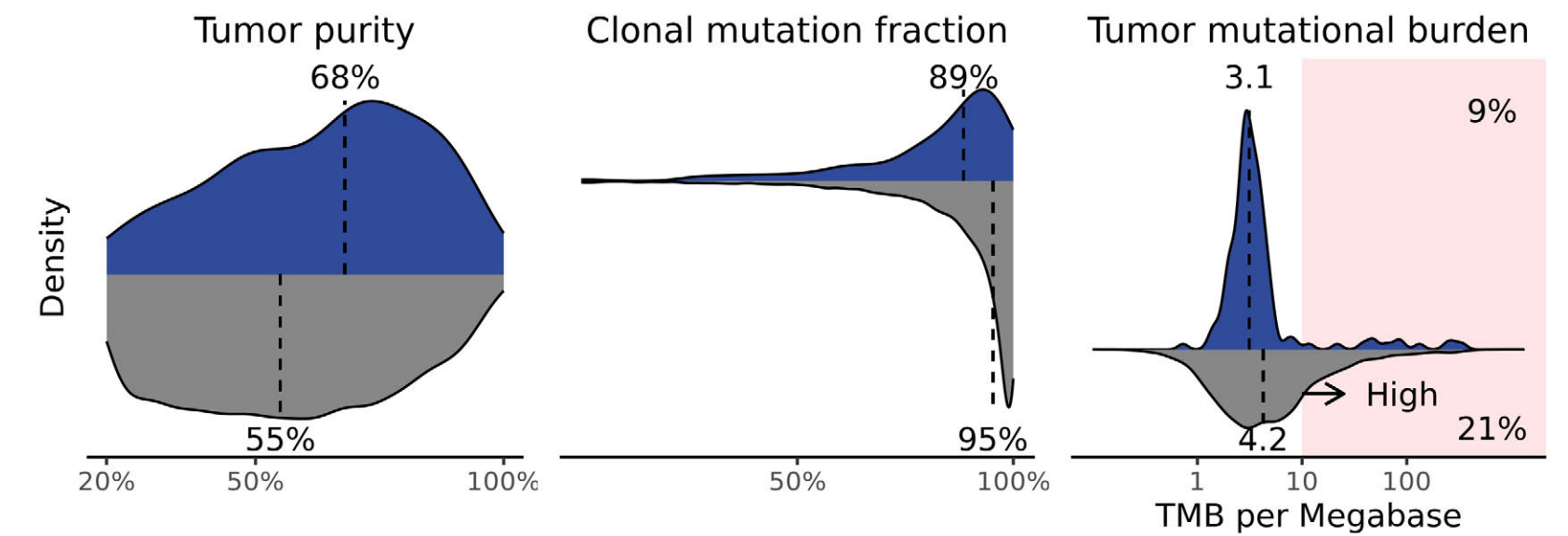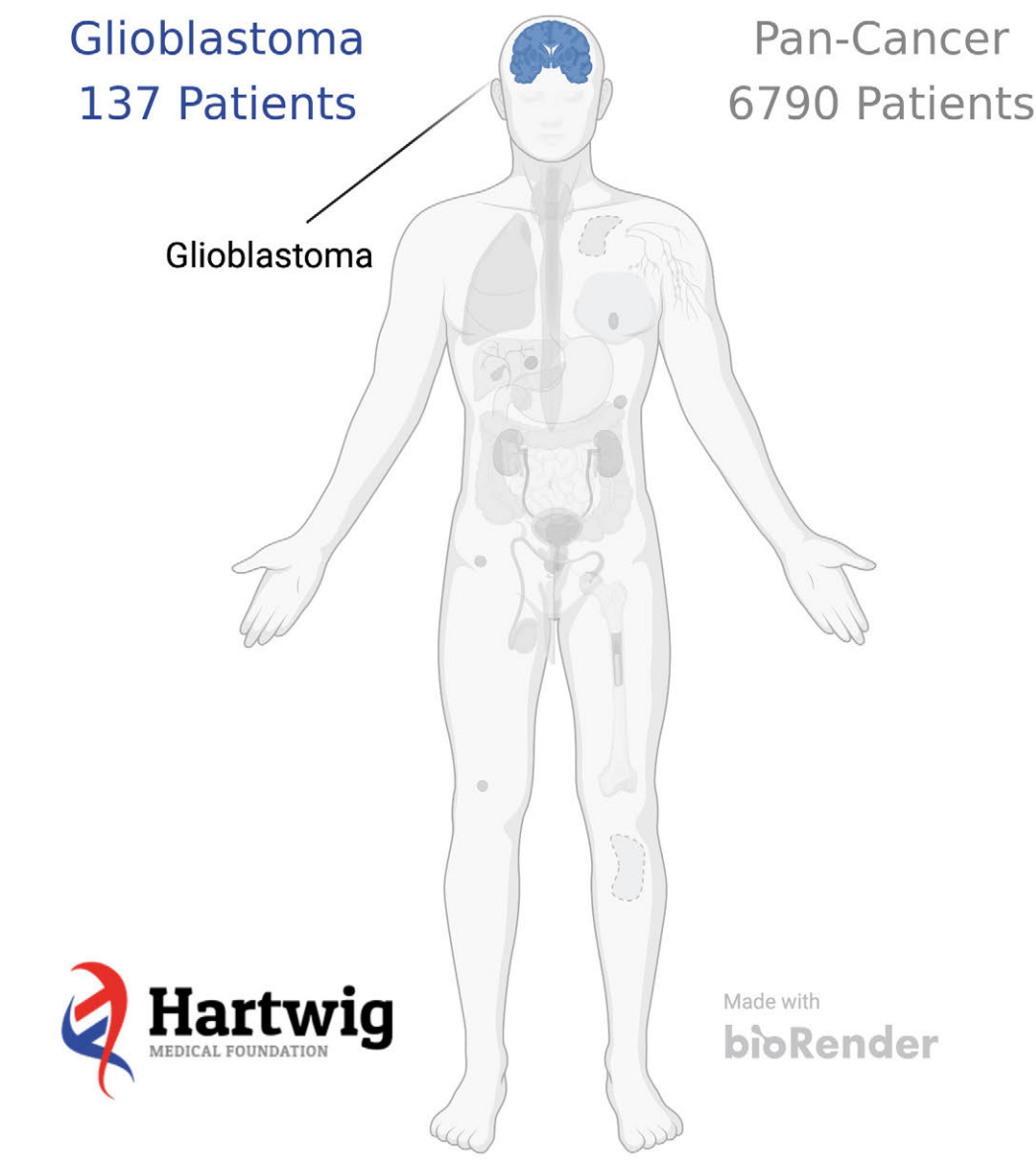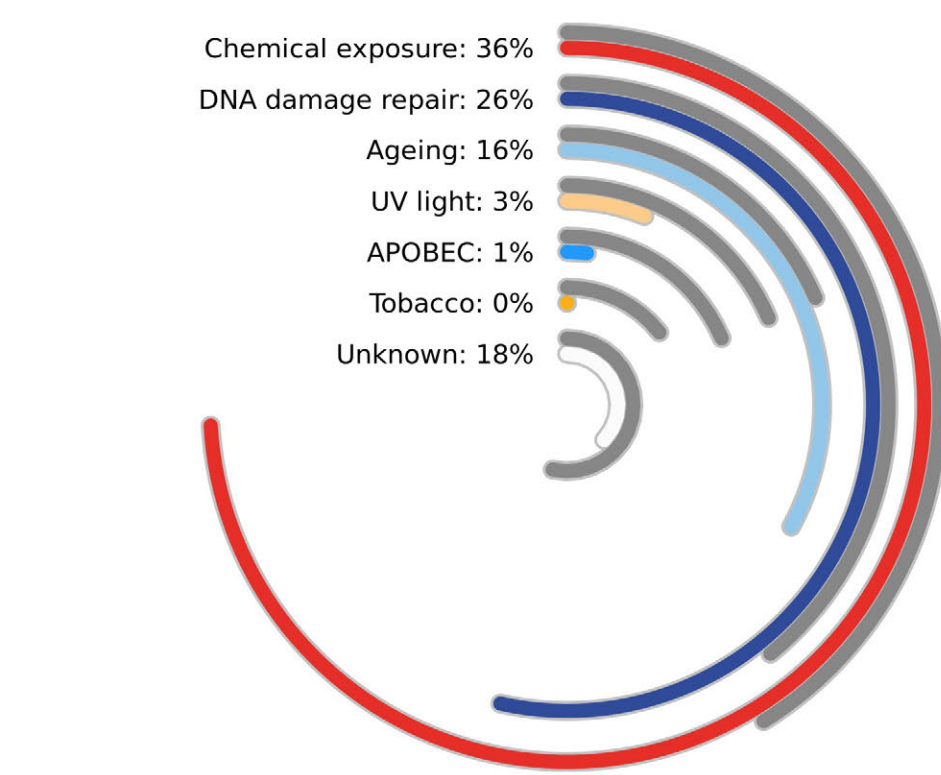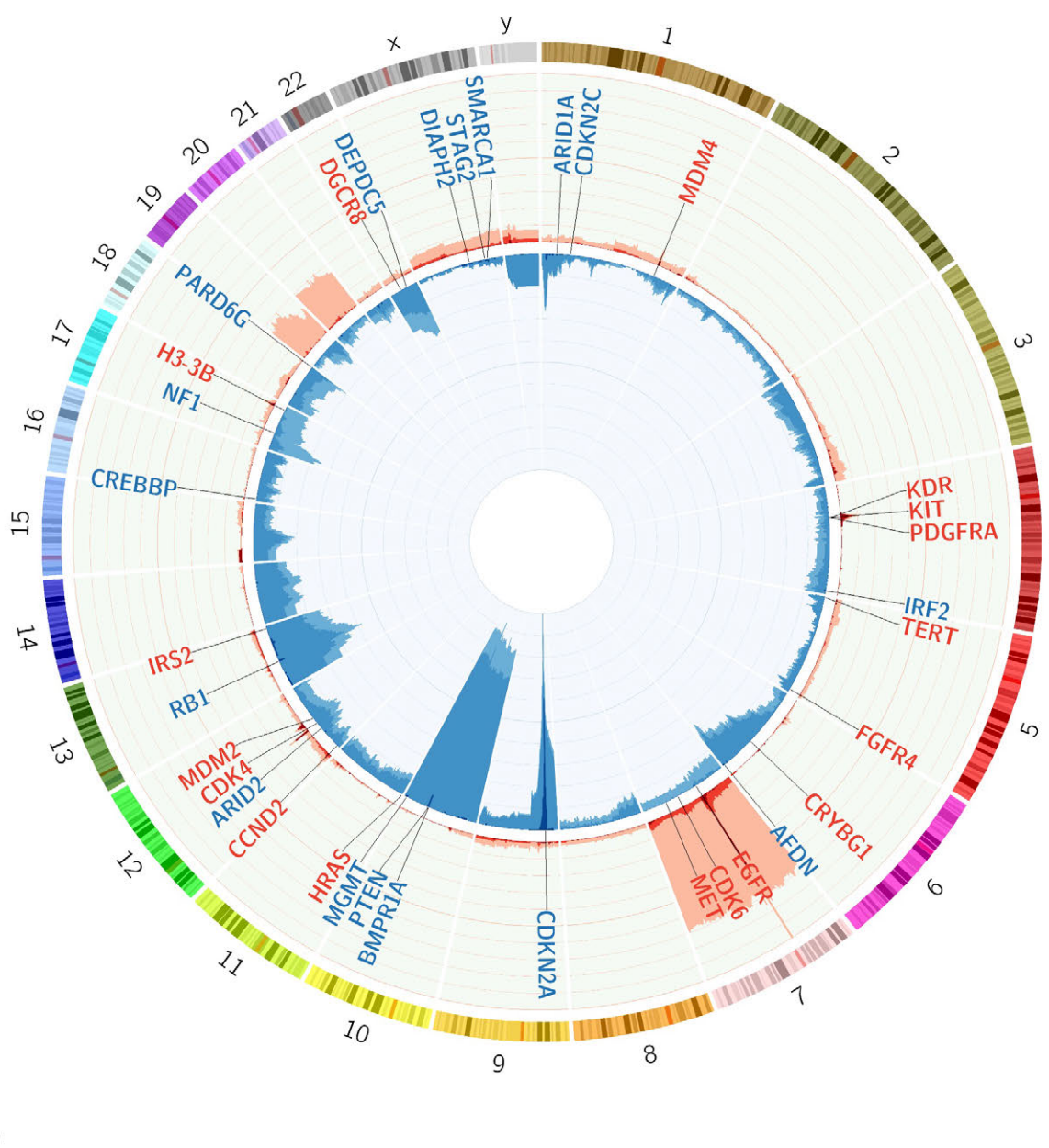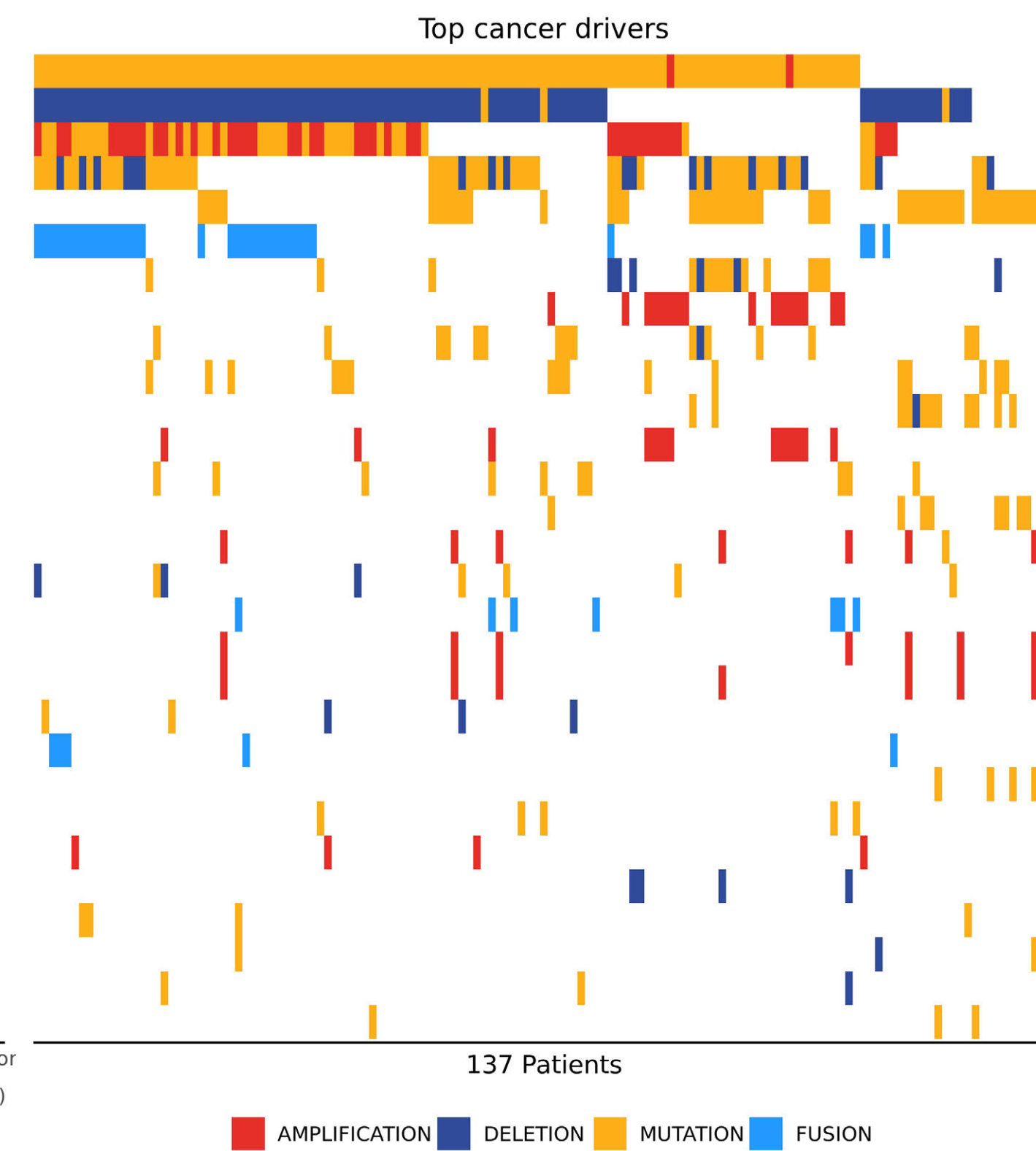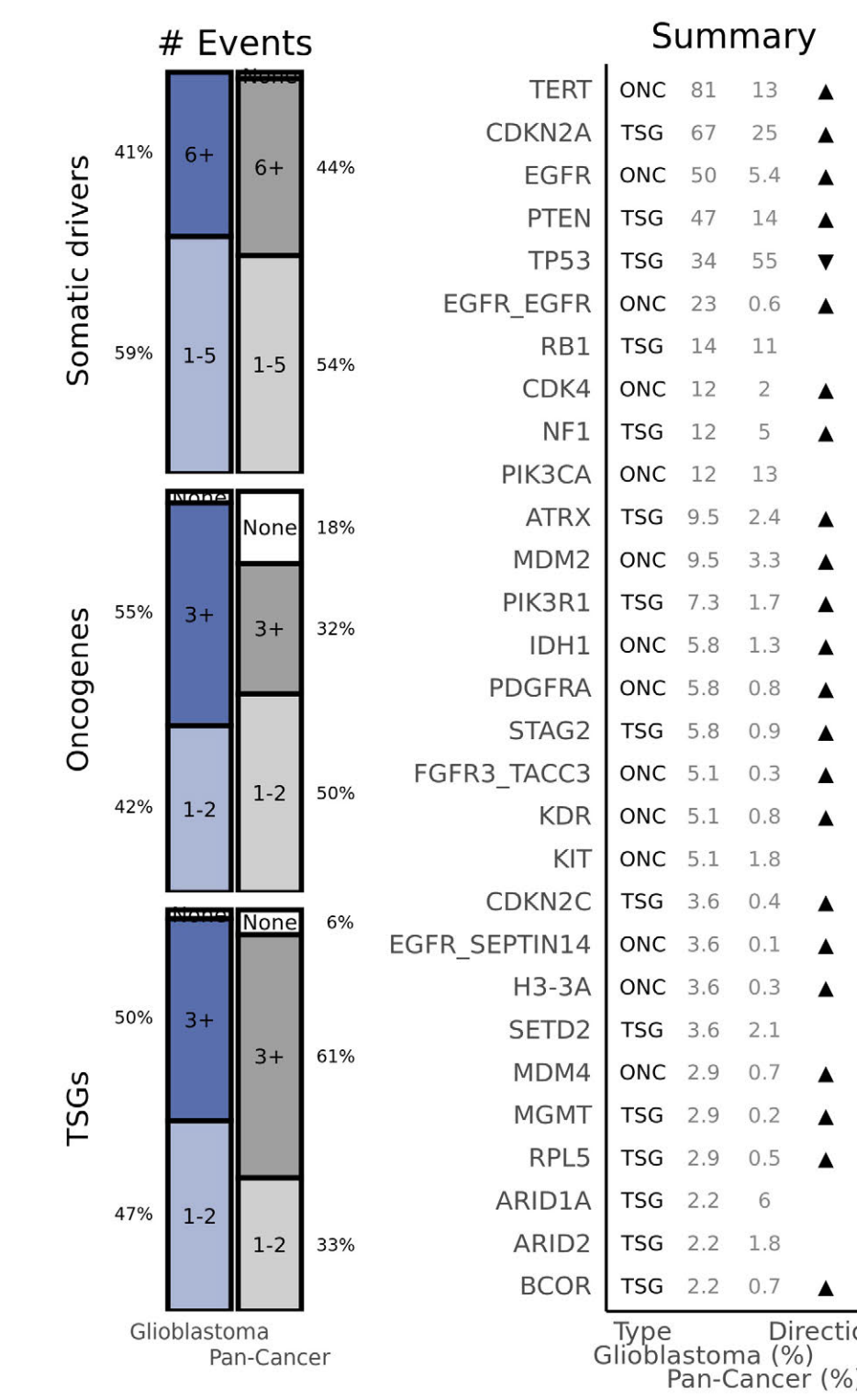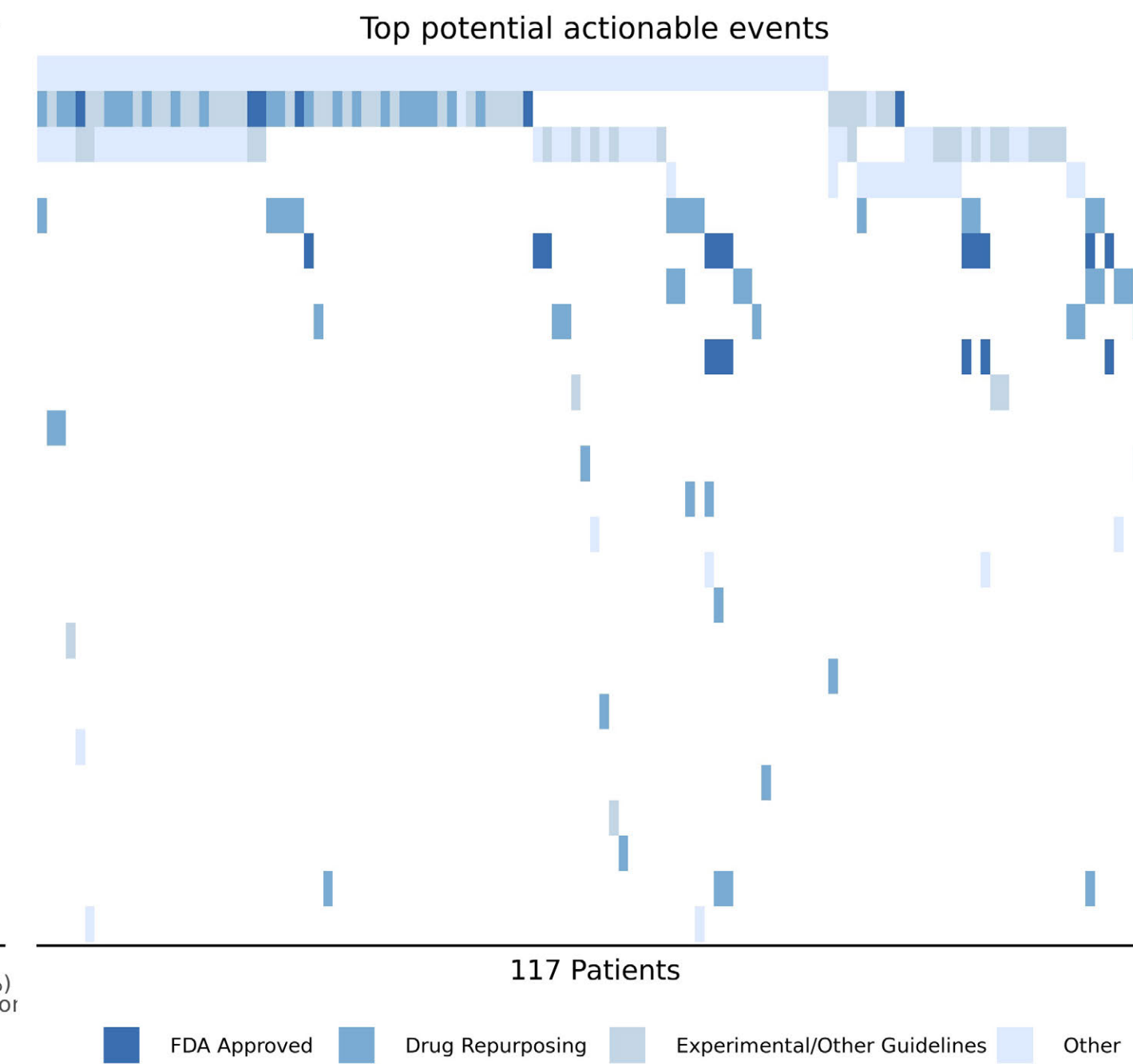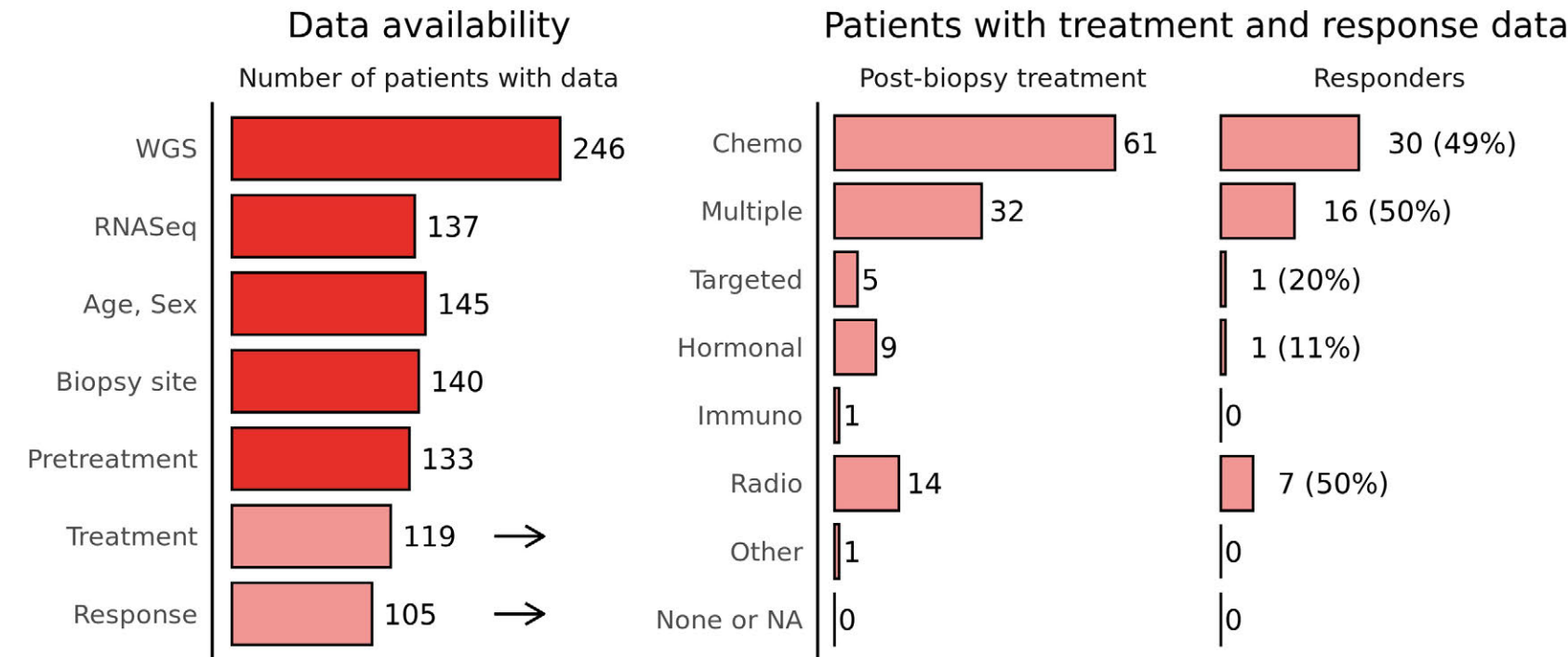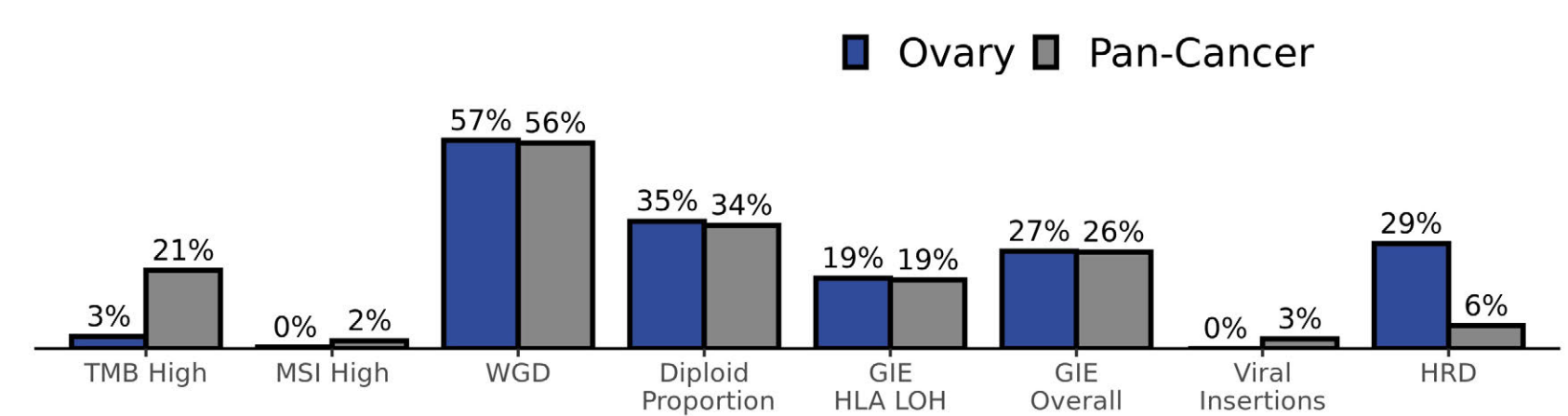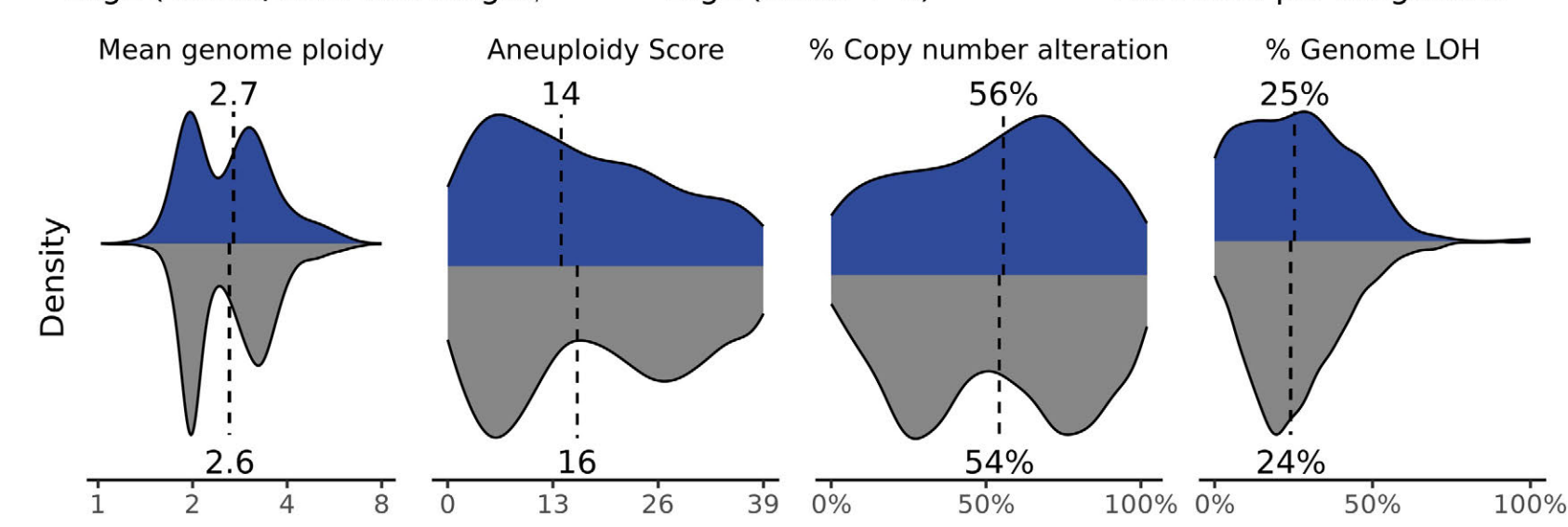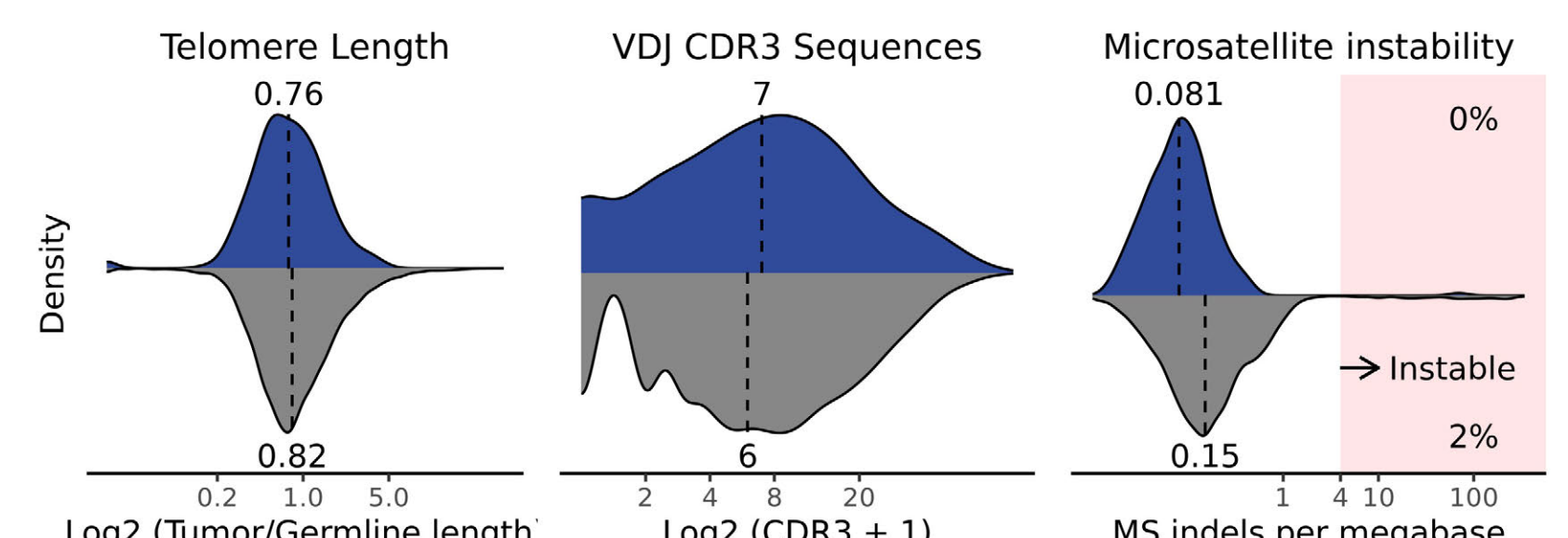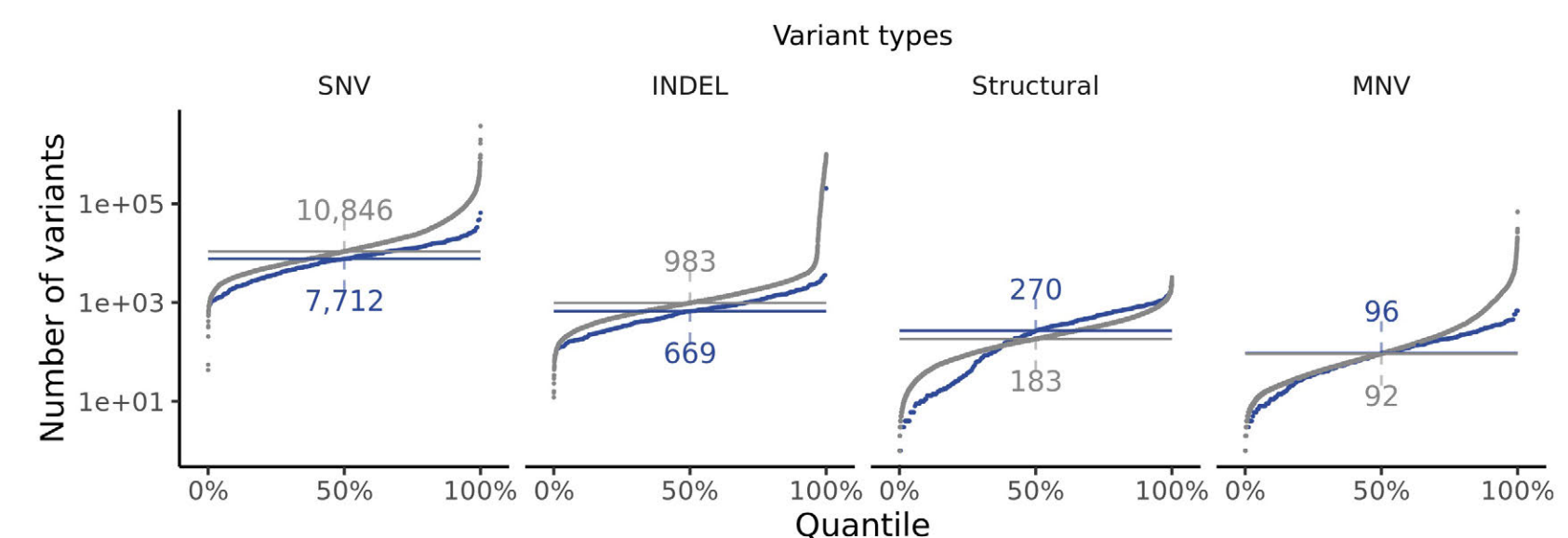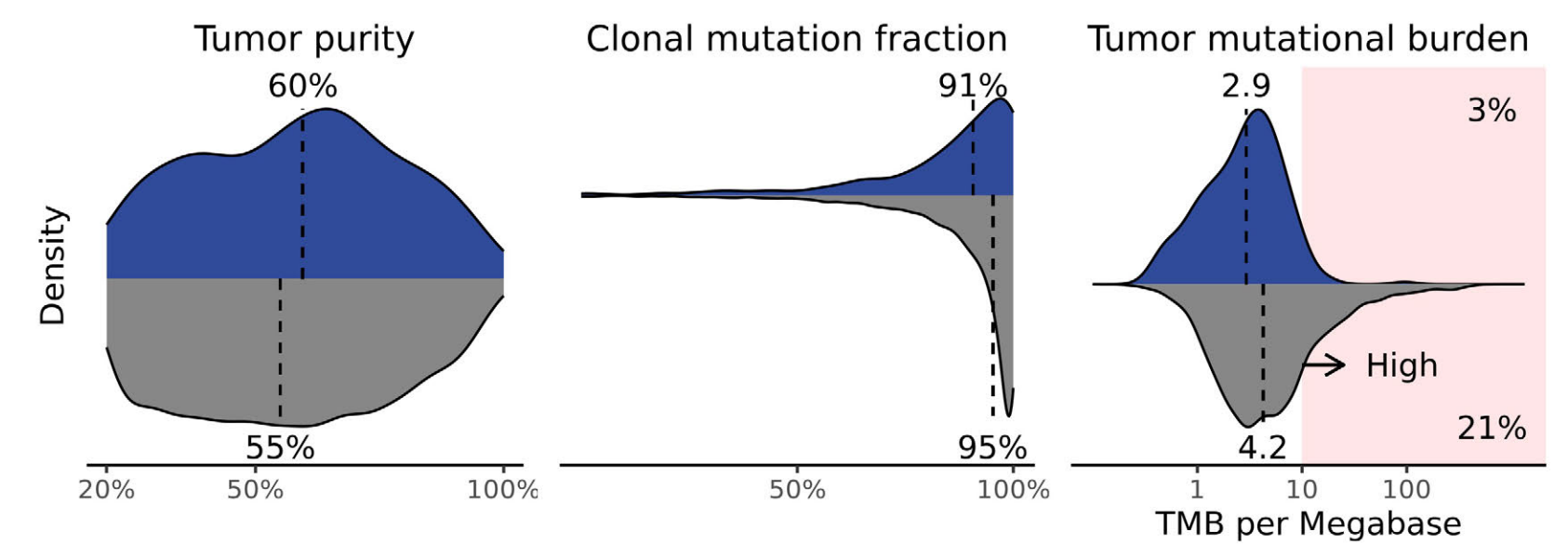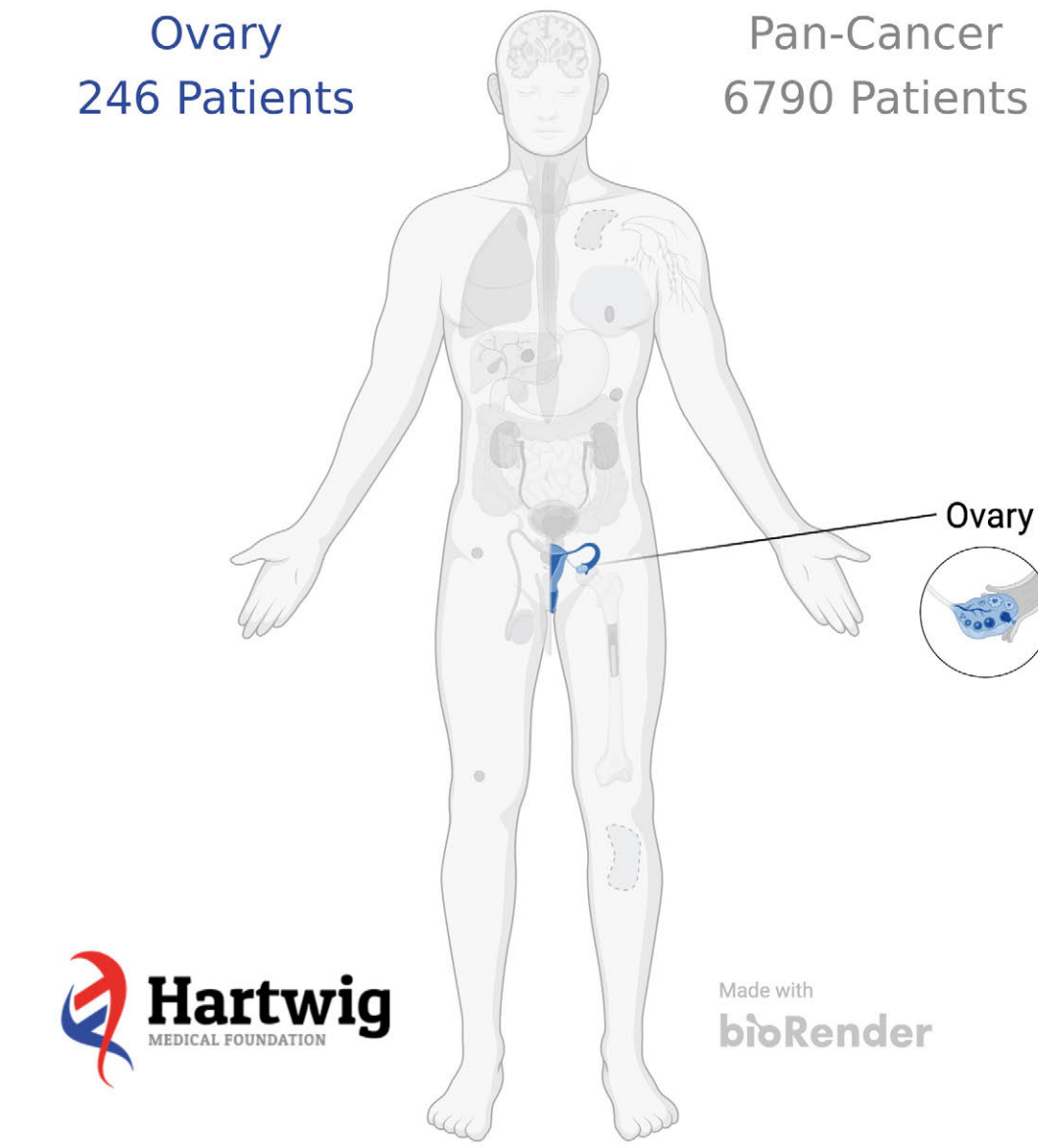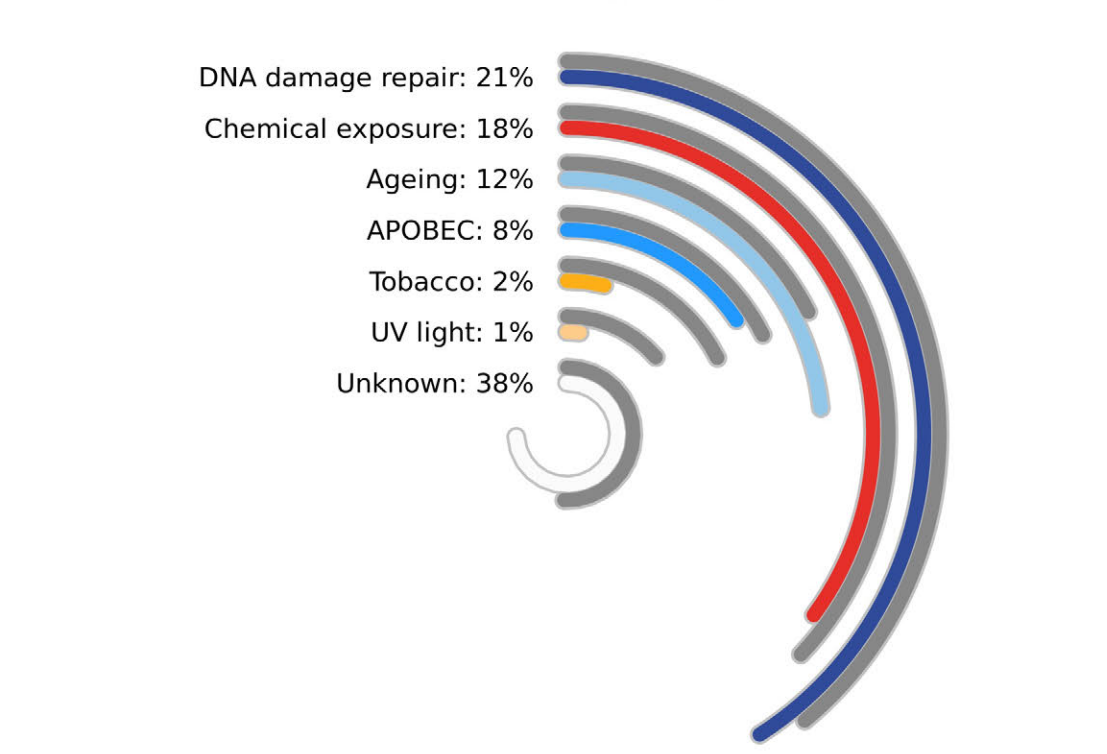** See documentation for further details on the WGS vs Panel coverage study.

Made with bioRender

# The Genomic And Actionability Landscape Of Glioblastoma Multiforme

## Cohort Metadata

### Data availability

Number of patients with data

| | |
|---|---|
| WGS | 137 |
| RNASeq | 59 |
| Age, Sex | 69 |
| Biopsy site | 69 |
| Pretreatment | 67 |
| Treatment | 54 → |
| Response | 0 → |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 1 | 0 |
| Multiple | 0 | 0 |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 1 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Glioblastoma, Pan-Cancer

| | TMB High | MSI High | WGD | Diploid Proportion | GIE HLA LOH | GIE Overall | Viral Insertions | HRD |
|---|---|---|---|---|---|---|---|---|
| Glioblastoma | 9% | 4% | 12% | 66% | 4% | 6% | 0% | 0% |
| Pan-Cancer | 21% | 2% | 56% | 34% | 19% | 26% | 3% | 6% |

## Mutational Landscape

### Tumor purity
68% / 55%

### Clonal mutation fraction
89% / 95%

### Tumor mutational burden
3.1 / 4.2, High, 9% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Glioblastoma | 8,166 | 822 | 120 | 47 |

Number of variants vs Quantile

### Telomere Length
1.1 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
2 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.12 / 0.15, Instable, 4% / 2%
MS indels per megabase

### Mean genome ploidy
2 / 2.6

### Aneuploidy Score
7 / 16

### % Copy number alteration
25% / 54%

### % Genome LOH
16% / 24%

## Processes Underlying Mutations

- Chemical exposure: 36%
- DNA damage repair: 26%
- Ageing: 16%
- UV light: 3%
- APOBEC: 1%
- Tobacco: 0%
- Unknown: 18%

Glioblastoma 137 Patients / Pan-Cancer 6790 Patients

Glioblastoma

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events

| Somatic drivers | | |
|---|---|---|
| 6+ | 41% | 44% (6+) |
| 1-5 | 59% | 54% (1-5) |

| Oncogenes | | |
|---|---|---|
| None | 18% | |
| 3+ | 55% | 32% (3+) |
| 1-2 | 42% | 50% (1-2) |

| TSGs | | |
|---|---|---|
| None | | |
| 3+ | 50% | 61% (3+) |
| 1-2 | 47% | 33% (1-2) |

### Summary

| Gene | Type | Glioblastoma (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|---|
| TERT | ONC | 81 | 13 | ▲ |
| CDKN2A | TSG | 67 | 25 | ▲ |
| EGFR | ONC | 50 | 5.4 | ▲ |
| PTEN | TSG | 47 | 14 | ▲ |
| TP53 | TSG | 34 | 55 | ▼ |
| EGFR_EGFR | ONC | 23 | 0.6 | ▲ |
| RB1 | TSG | 14 | 11 | |
| CDK4 | ONC | 12 | 2 | ▲ |
| NF1 | TSG | 12 | 5 | ▲ |
| PIK3CA | ONC | 12 | 13 | |
| ATRX | TSG | 9.5 | 2.4 | ▲ |
| MDM2 | ONC | 9.5 | 3.3 | ▲ |
| PIK3R1 | TSG | 7.3 | 1.7 | ▲ |
| IDH1 | ONC | 5.8 | 1.3 | ▲ |
| PDGFRA | ONC | 5.8 | 0.8 | ▲ |
| STAG2 | TSG | 5.8 | 0.9 | ▲ |
| FGFR3_TACC3 | ONC | 5.1 | 0.3 | ▲ |
| KDR | ONC | 5.1 | 0.8 | ▲ |
| KIT | ONC | 5.1 | 1.8 | |
| CDKN2C | TSG | 3.6 | 0.4 | ▲ |
| EGFR_SEPTIN14 | ONC | 3.6 | 0.1 | ▲ |
| H3-3A | ONC | 3.6 | 0.3 | ▲ |
| SETD2 | TSG | 3.6 | 2.1 | |
| MDM4 | ONC | 2.9 | 0.7 | ▲ |
| MGMT | TSG | 2.9 | 0.2 | ▲ |
| RPL5 | TSG | 2.9 | 0.5 | ▲ |
| ARID1A | TSG | 2.2 | 6 | |
| ARID2 | TSG | 2.2 | 1.8 | |
| BCOR | TSG | 2.2 | 5 | |

Glioblastoma / Pan-Cancer

Top cancer drivers — 137 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events

| Actionable | | |
|---|---|---|
| None | 15% | 18% |
| 3+ | 39% | 26% |
| 1-2 | 46% | 56% |

| Best treatment option | | |
|---|---|---|
| None | 15% | 18% |
| Oth | 12% | 14% |
| Exp | | 5% |
| Off | 33% | 28% |
| FDA | 12% | 36% |

### Summary

| Event | Glioblastoma (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|
| CDKN2A | 61 | 24 | |
| EGFR | 44 | 5.1 | ▲ |
| PTEN | 42 | 13 | ▲ |
| CDK4 | 11 | 1.9 | ▲ |
| PIK3CA | 10 | 13 | |
| TMB High | 8 | 21 | ▼ |
| IDH1 | 5.8 | 1 | ▲ |
| FGFR3 - TACC3 fusion | 5.1 | 0.3 | ▲ |
| MSI High | 4.4 | 3.1 | |
| NF1 | 2.2 | 0.4 | ▲ |
| CHEK2 | 1.5 | 3 | |
| FGFR3 | 1.5 | 1.2 | |
| MET | 1.5 | 1.7 | |
| TSC1 | 1.5 | 1.1 | |
| TSC2 | 1.5 | 0.8 | |
| ATM | 0.7 | 3.5 | ▼ |
| BRAF | 0.7 | 5.9 | ▼ |
| BRCA1 | 0.7 | 1.3 | |
| CCDC6 - RET fusion | 0.7 | 0.1 | |
| CTNNB1 | 0.7 | 1.7 | ▼ |
| DTD1 - BRAF fusion | 0.7 | 0 | ▲ |
| FGFR1 | 0.7 | 3.8 | ▼ |
| GOPC - ROS1 fusion | 0.7 | 0.1 | ▲ |
| Rest Repurpose | 2.9 | | |
| Rest Other | 2.2 | | |

Glioblastoma / Pan-Cancer

Top potential actionable events — 117 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

| Germline drivers | | |
|---|---|---|
| None | 88% | 84% |
| 1+ | 12% | 16% |

### Summary

| Gene | Type | Glioblastoma (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|---|
| CHEK2 | TSG | 2.2 | 3.2 | |
| MSH6 | TSG | 2.2 | 0.4 | ▲ |
| PMS2 | TSG | 2.2 | 0.5 | ▲ |
| MUTYH | TSG | 1.5 | 1.9 | |
| ATM | TSG | 0.7 | 1 | |
| BRCA1 | TSG | 0.7 | 1.1 | |
| MITF | ONC | 0.7 | 0.7 | |
| MSH2 | TSG | 0.7 | 1 | |
| RAD54L | TSG | 0.7 | 0.4 | |

Glioblastoma / Pan-Cancer

Top potential germline drivers — 15 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| Strategy | | | | | |
|---|---|---|---|---|---|
| WGS | 17 | 45 | 47 | 11 | 17 |
| Comprehensive 521 gene panel | 17 | 35 | 46 | 18 | 21 |
| Targeted 50 gene panel | 11 | 32 | 40 | 20 | 34 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | Total |
|---|---|---|---|---|
| WGS | 0.61 | 0.85 | 0.91 | 2.5 |
| Comprehensive 521 gene panel | 0.54 | 0.69 | 0.83 | 2.2 |
| Targeted 50 gene panel | 0.34 | 0.51 | 0.7 | 1.6 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved / Drug Repurposing

| | |
|---|---|
| Fusion | 10 |

Experimental/Other Guidelines / Other

| | | | |
|---|---|---|---|
| Partial CN Loss | 10 | Partial CN Loss | 6 |
| Partial CN Gain | 10 | HMZ Disruption | 2 |
| Full CN Gain | 1 | Small Variant | 1 |
| HMZ Disruption | 1 | Full CN Loss | 1 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved / Drug Repurposing

| | | | |
|---|---|---|---|
| TMB High | 11 | Small Variant | 27 |
| Small Variant | 1 | Fusion | 10 |

Experimental/Other Guidelines / Other

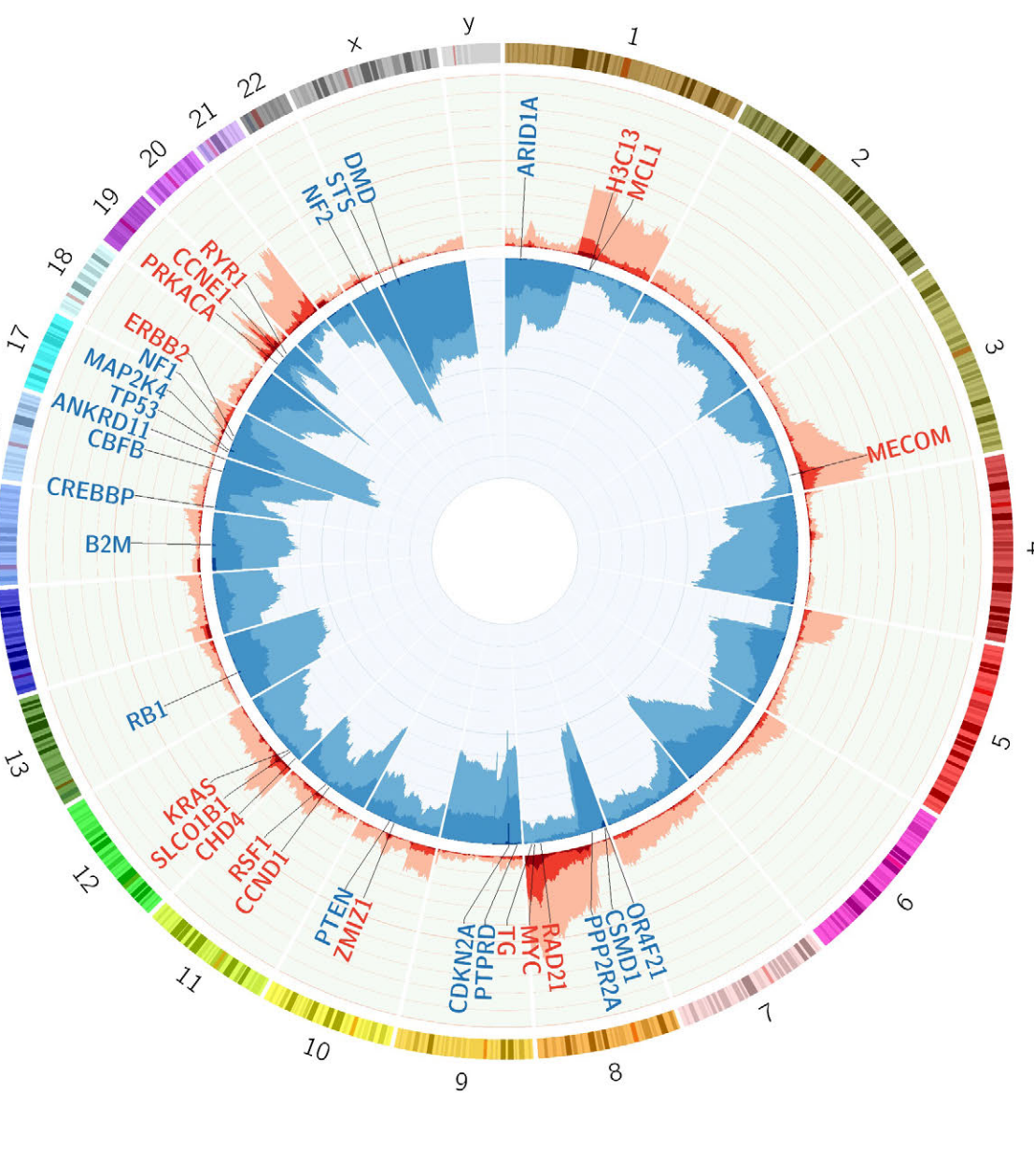| | | | |
|---|---|---|---|
| Full CN Gain | 19 | Small Variant | 17 |
| Partial CN Loss | 10 | Partial CN Loss | 6 |
| Partial CN Gain | 10 | HMZ Disruption | 2 |
| Small Variant | 6 | Splice Site | 2 |
| HMZ Disruption | 1 | Full CN Loss | 1 |

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
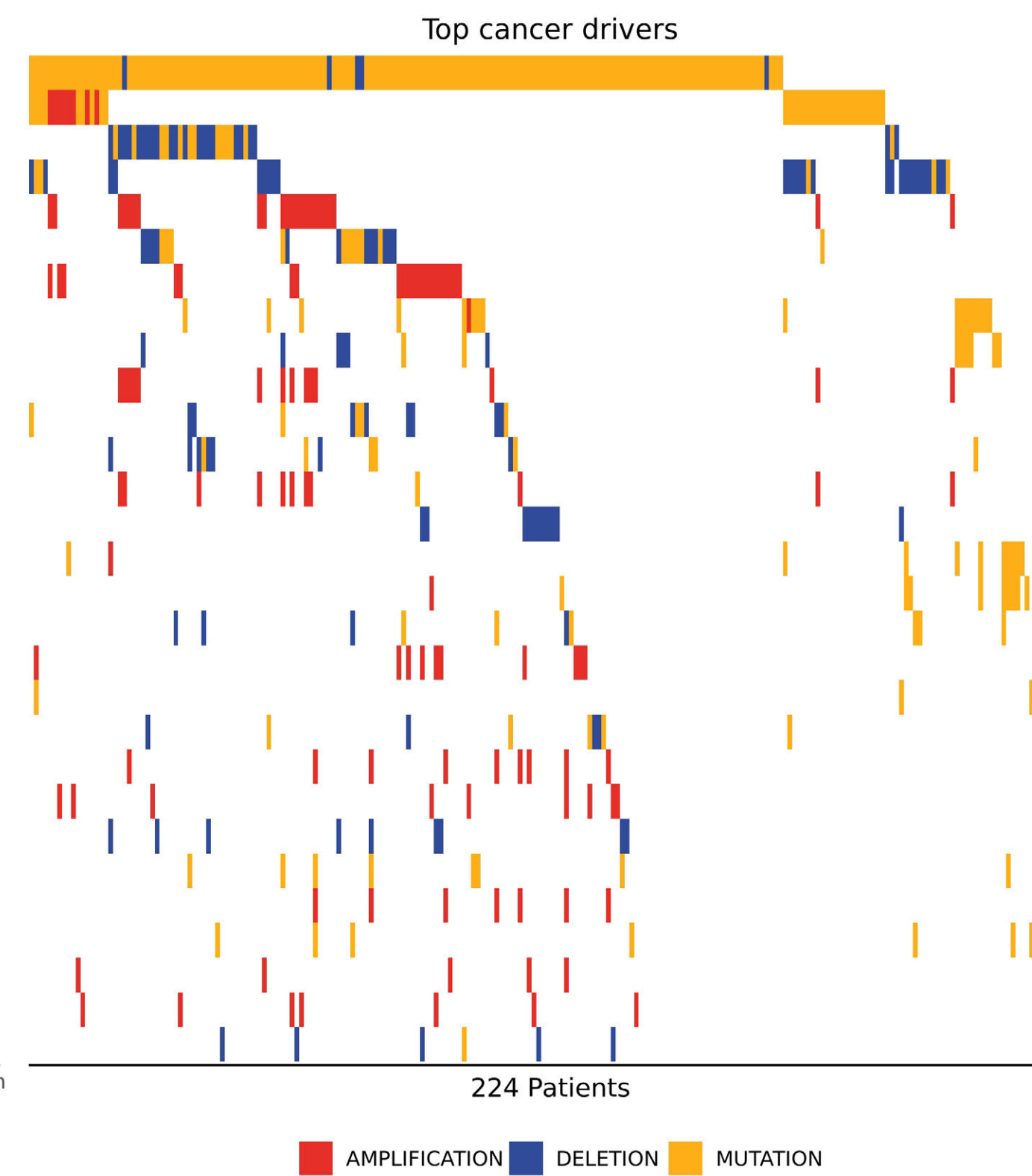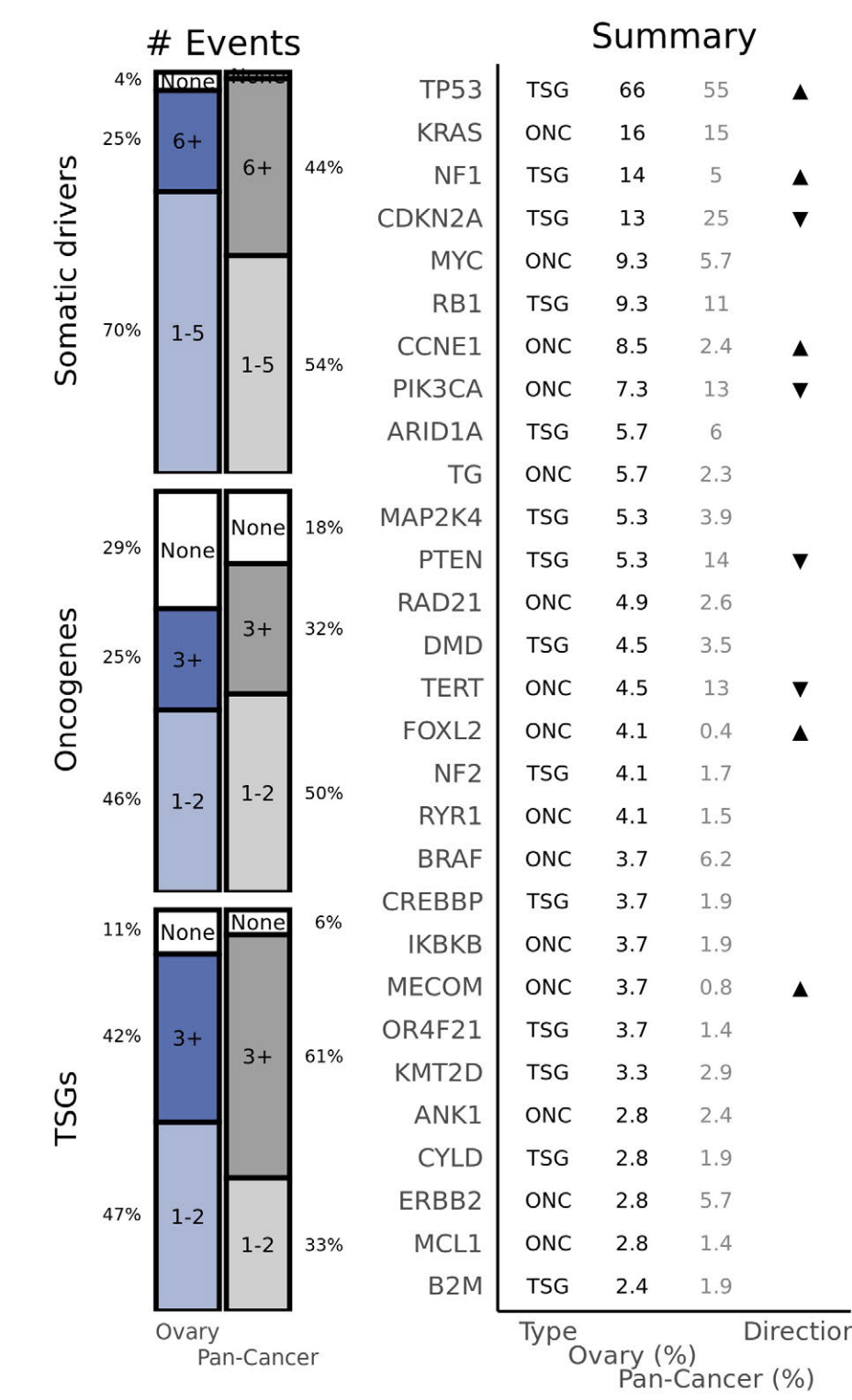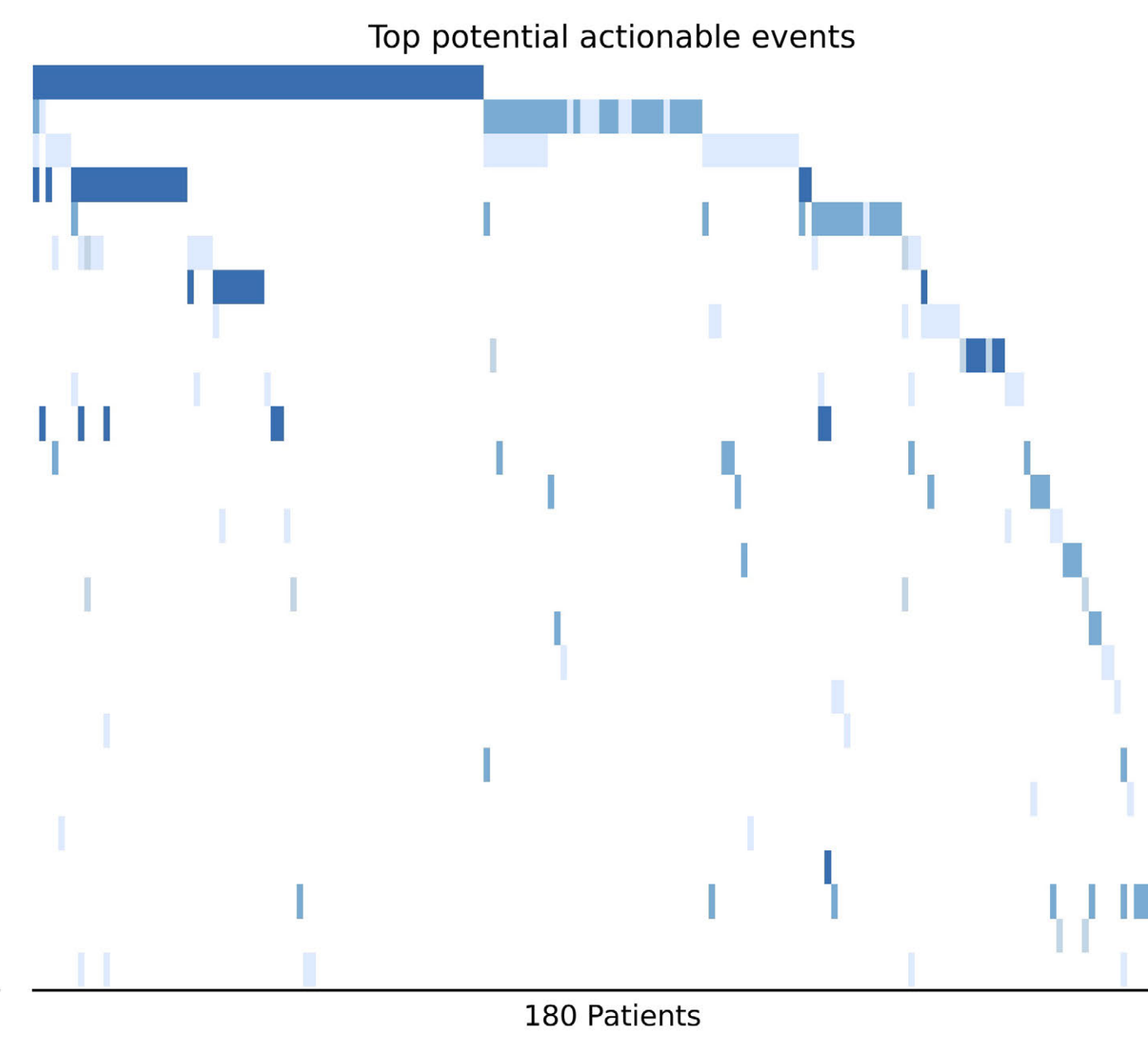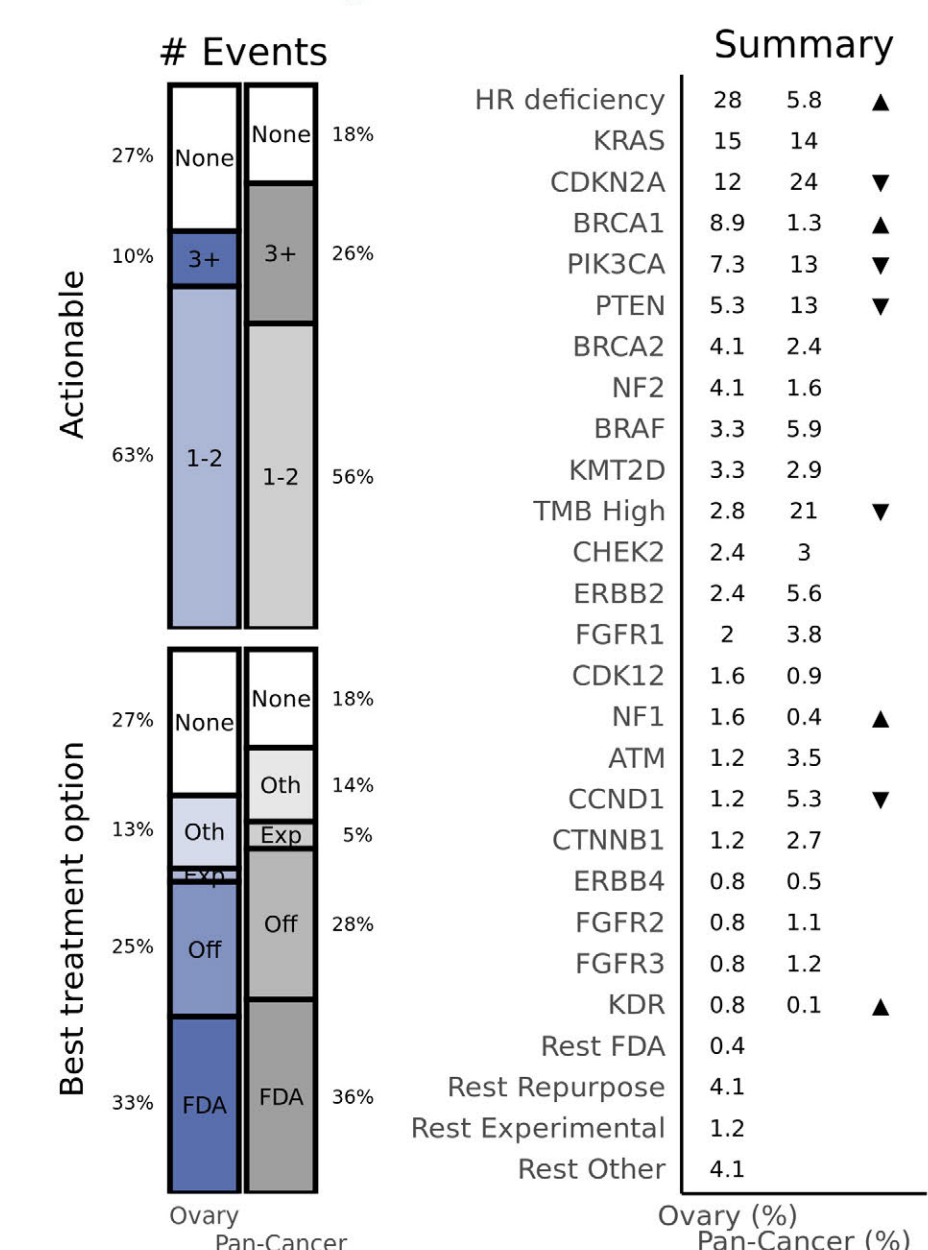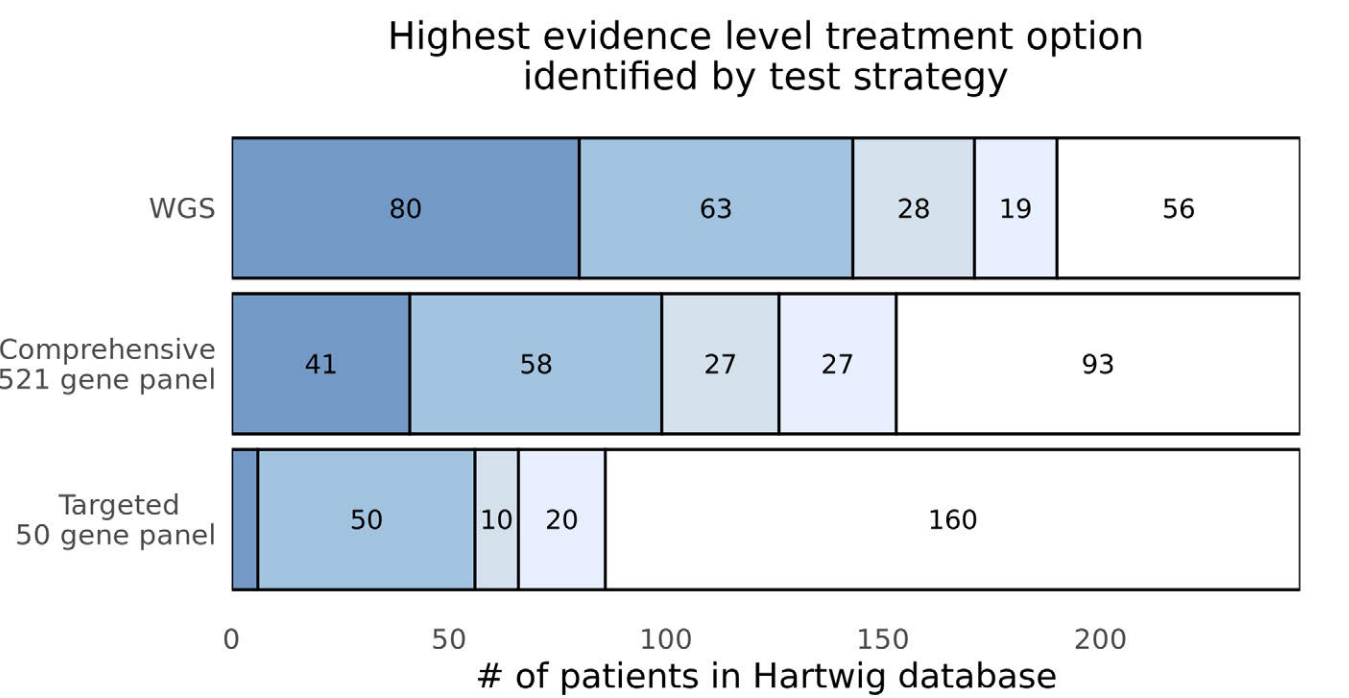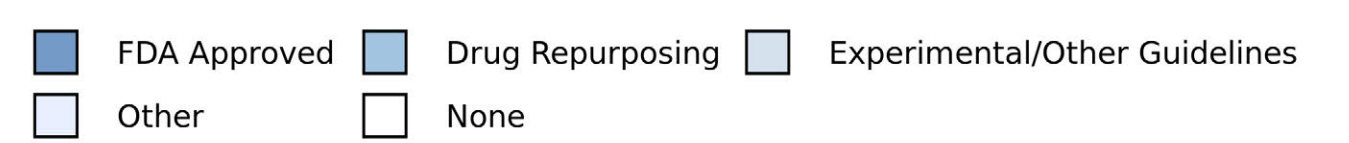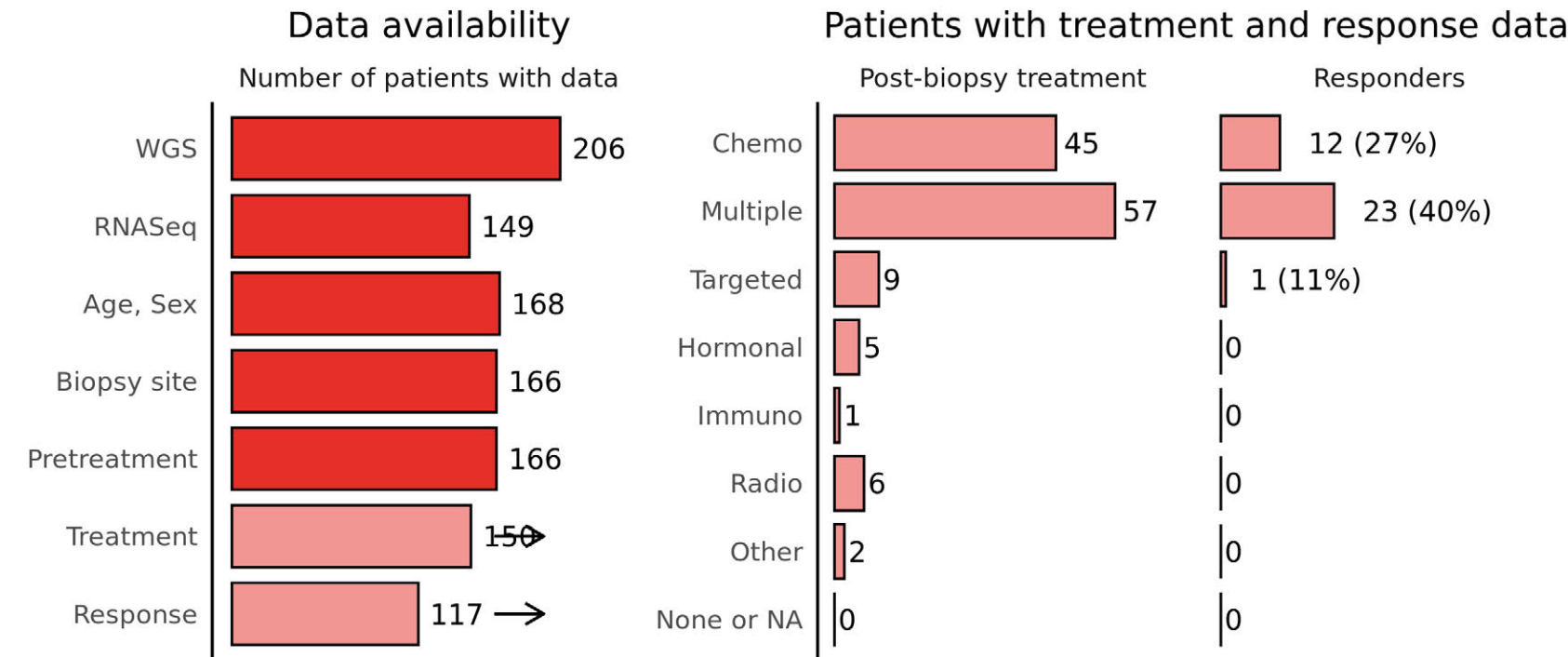Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

### Acronym: GBM
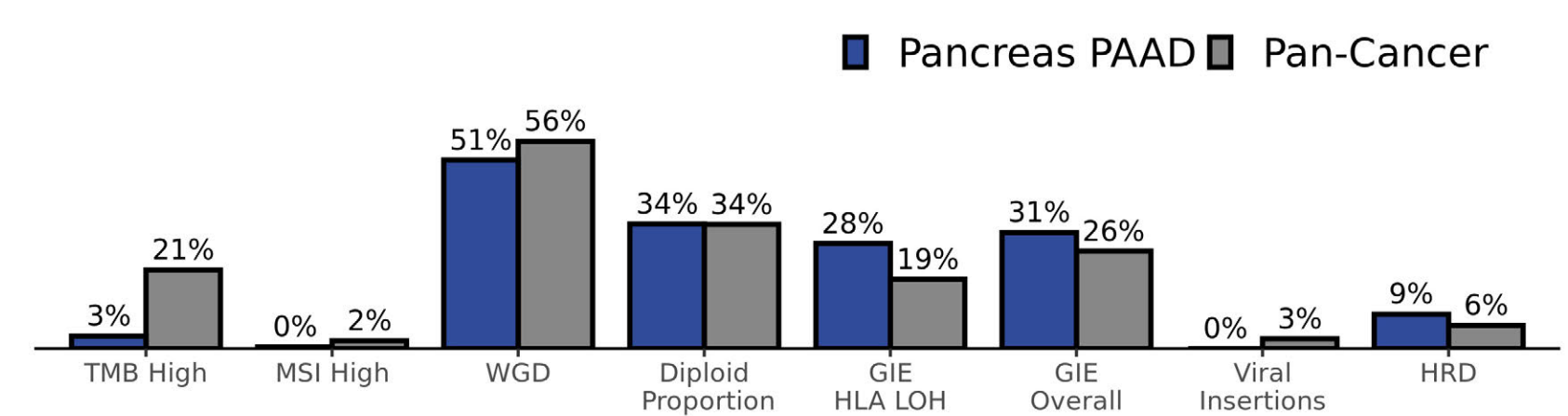DOIDs included: 3068, 3073, 3070
Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic platforms. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with: min copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Disruptions, Viral inserts, HLA type assumed not captured by panels.
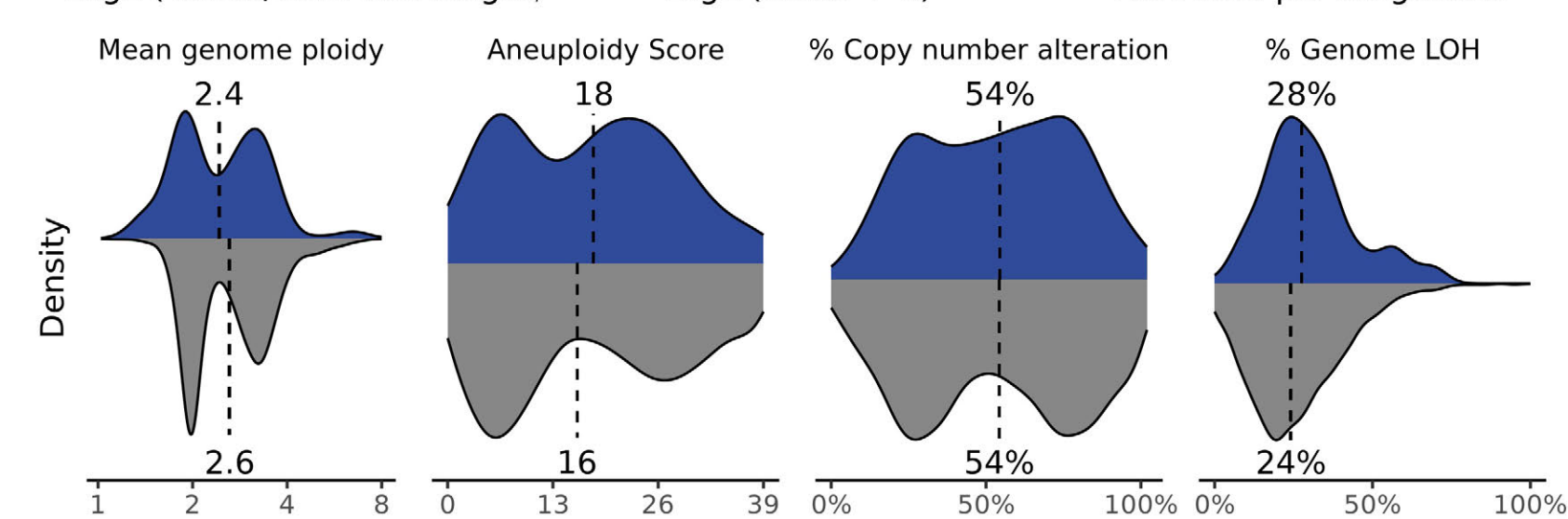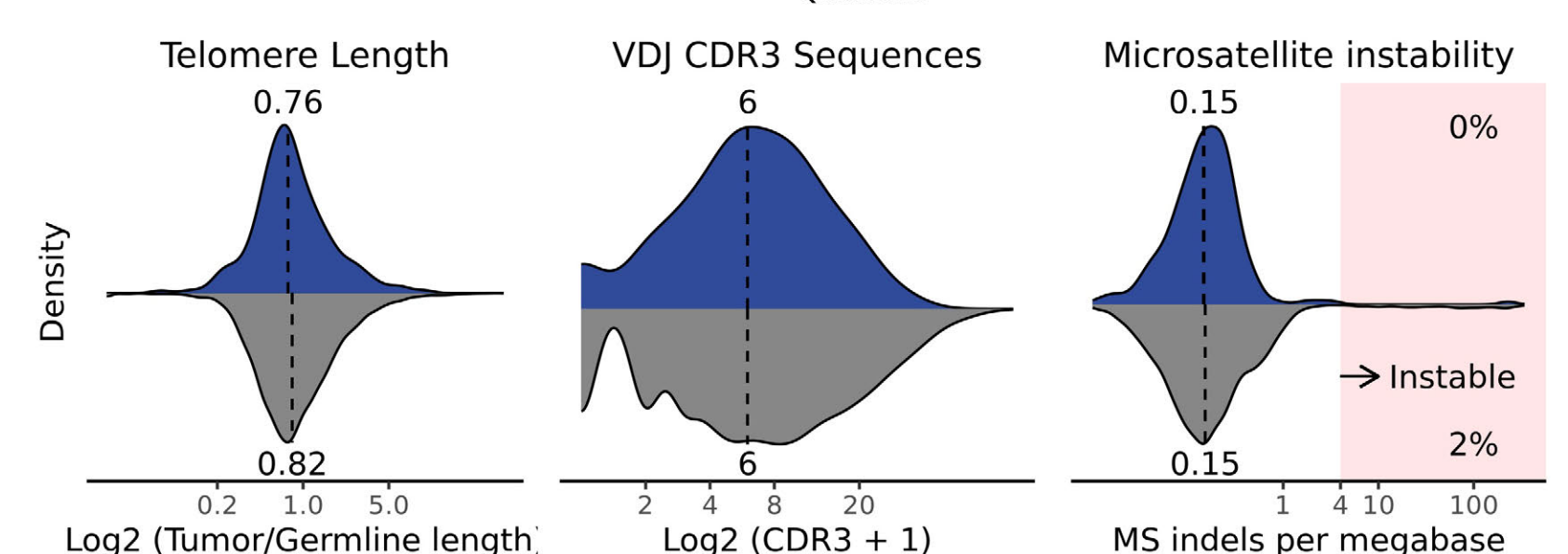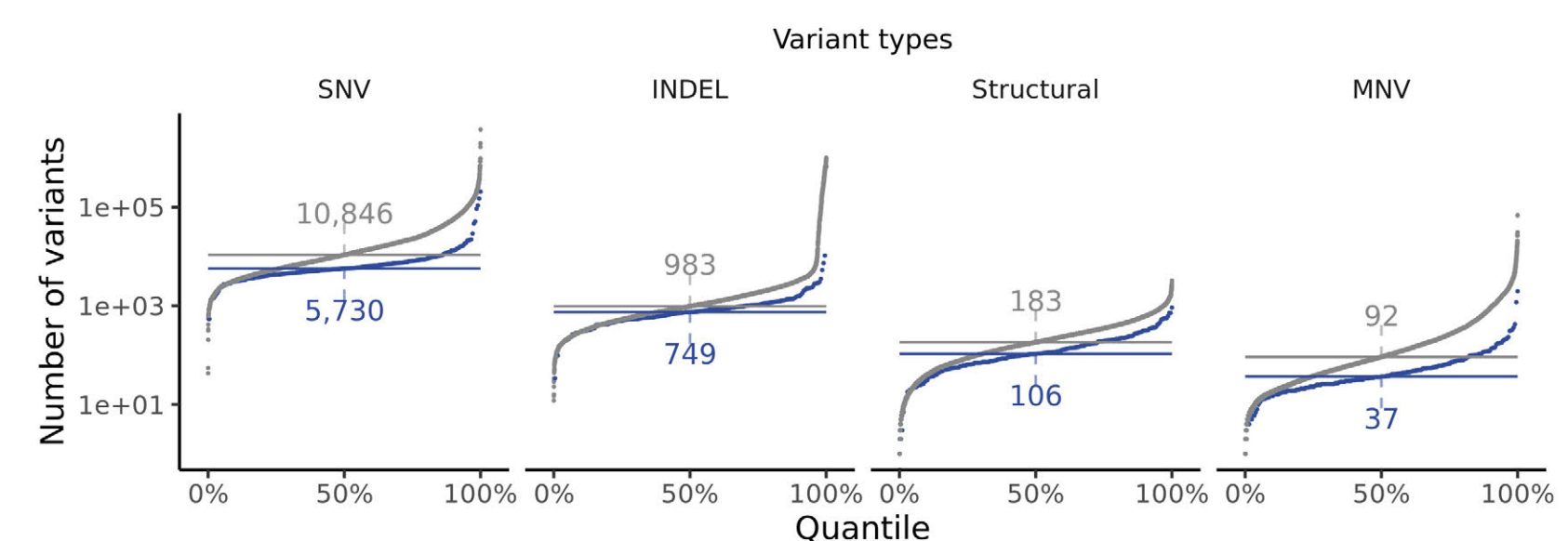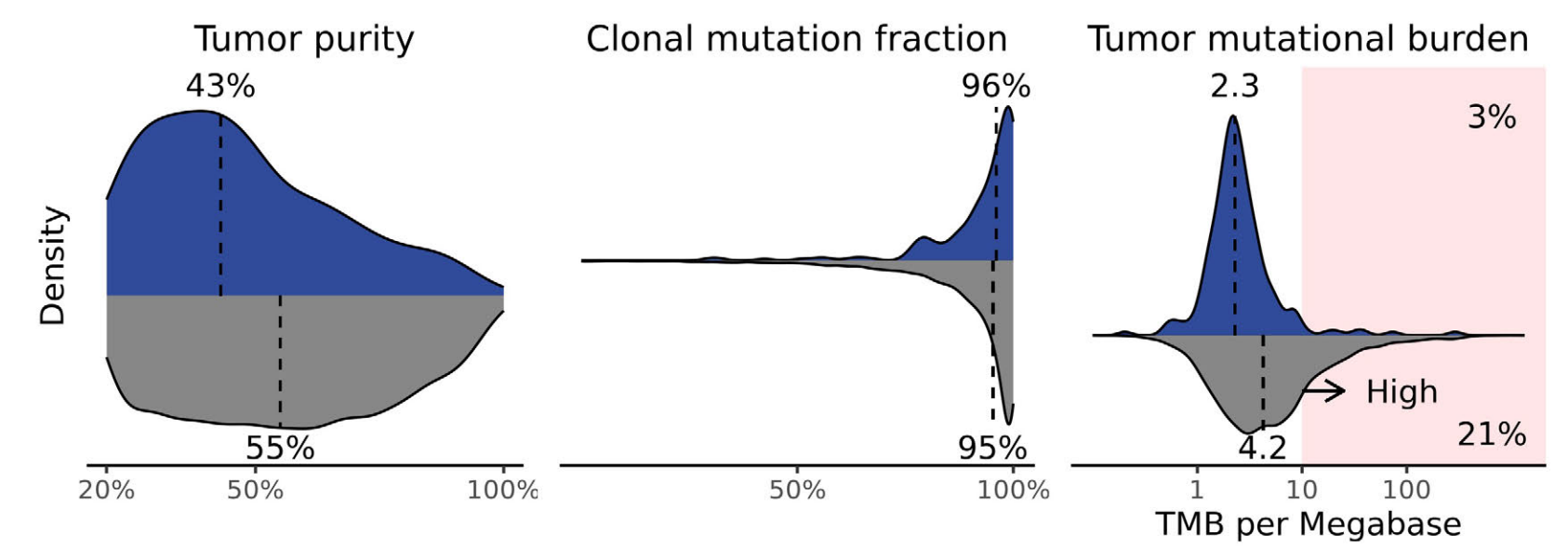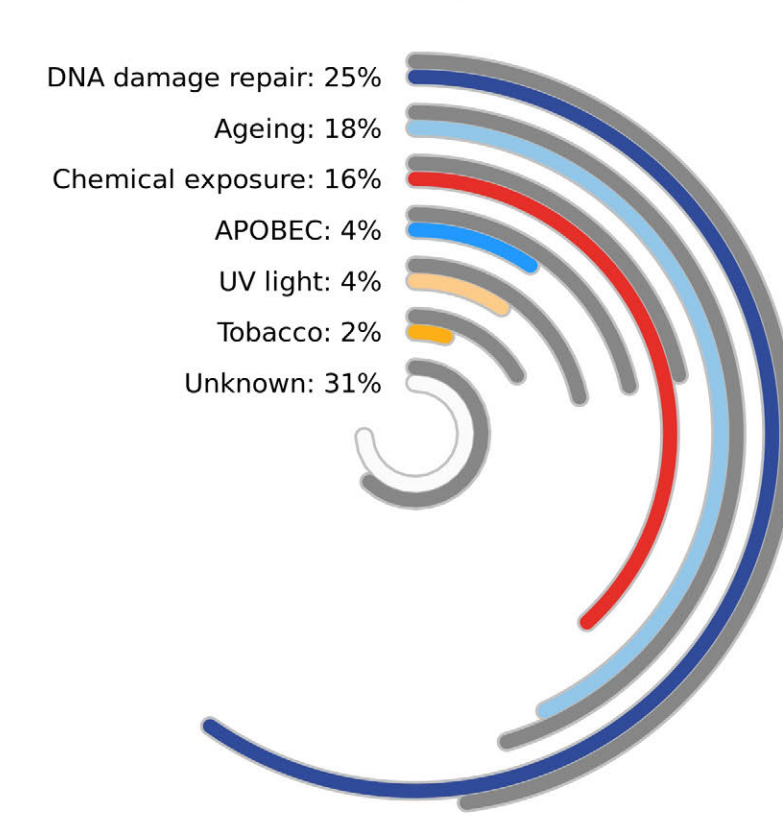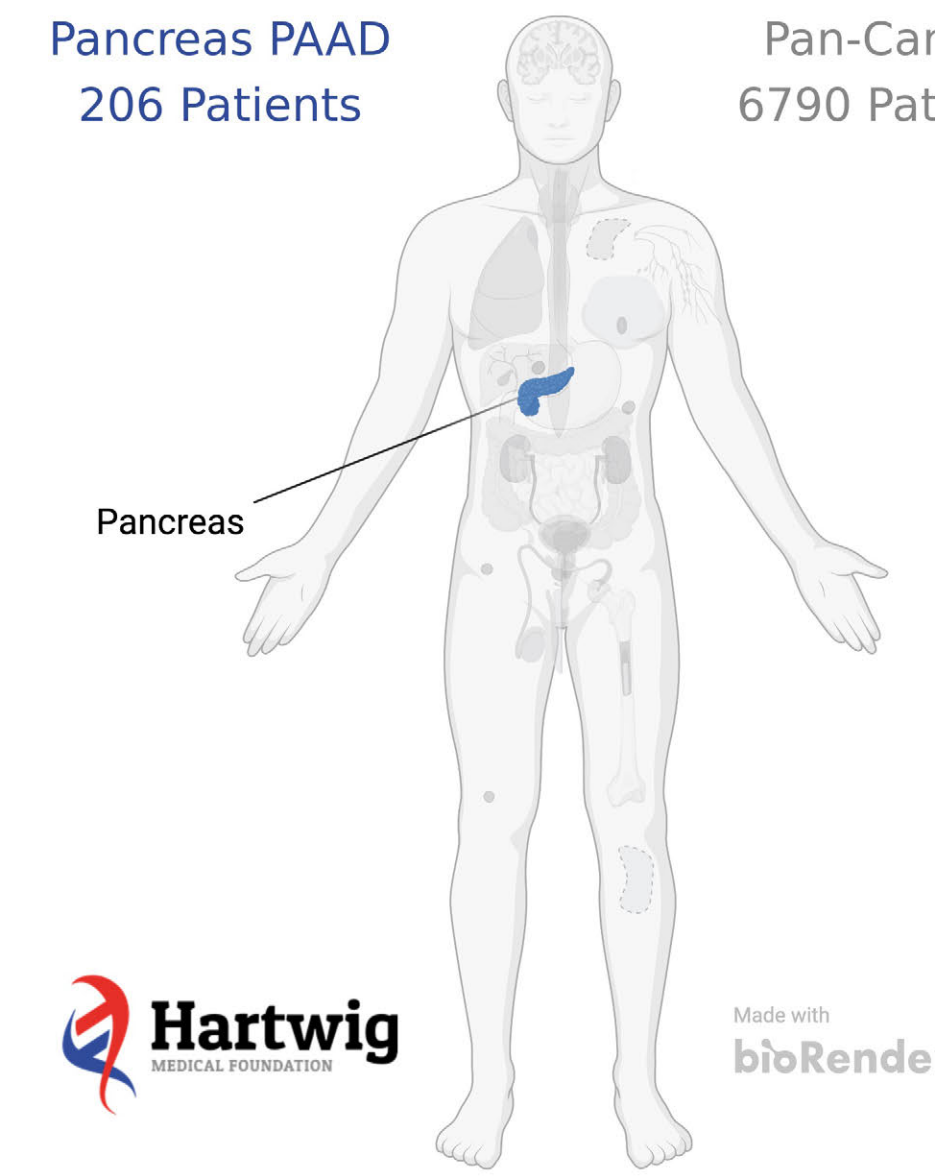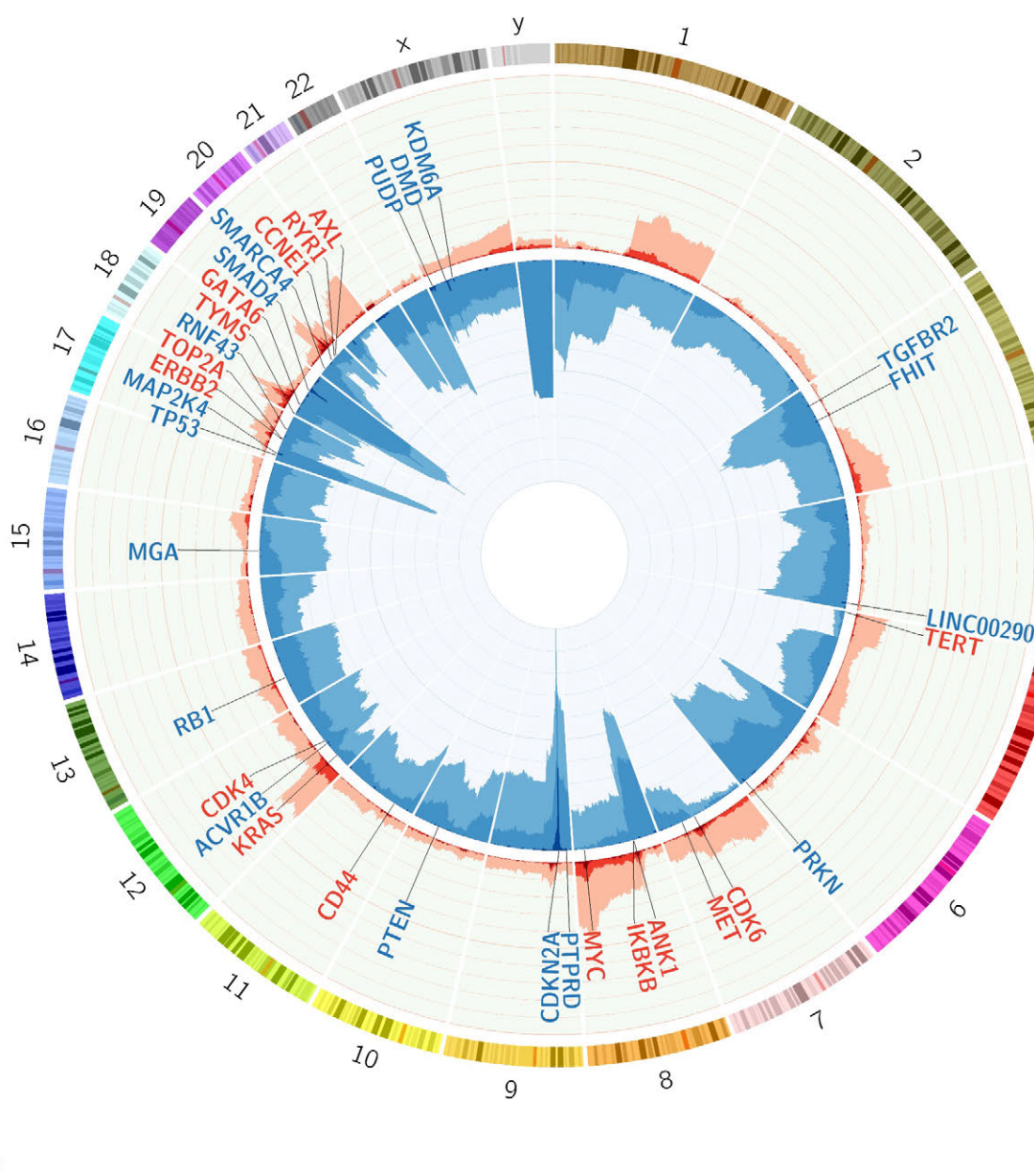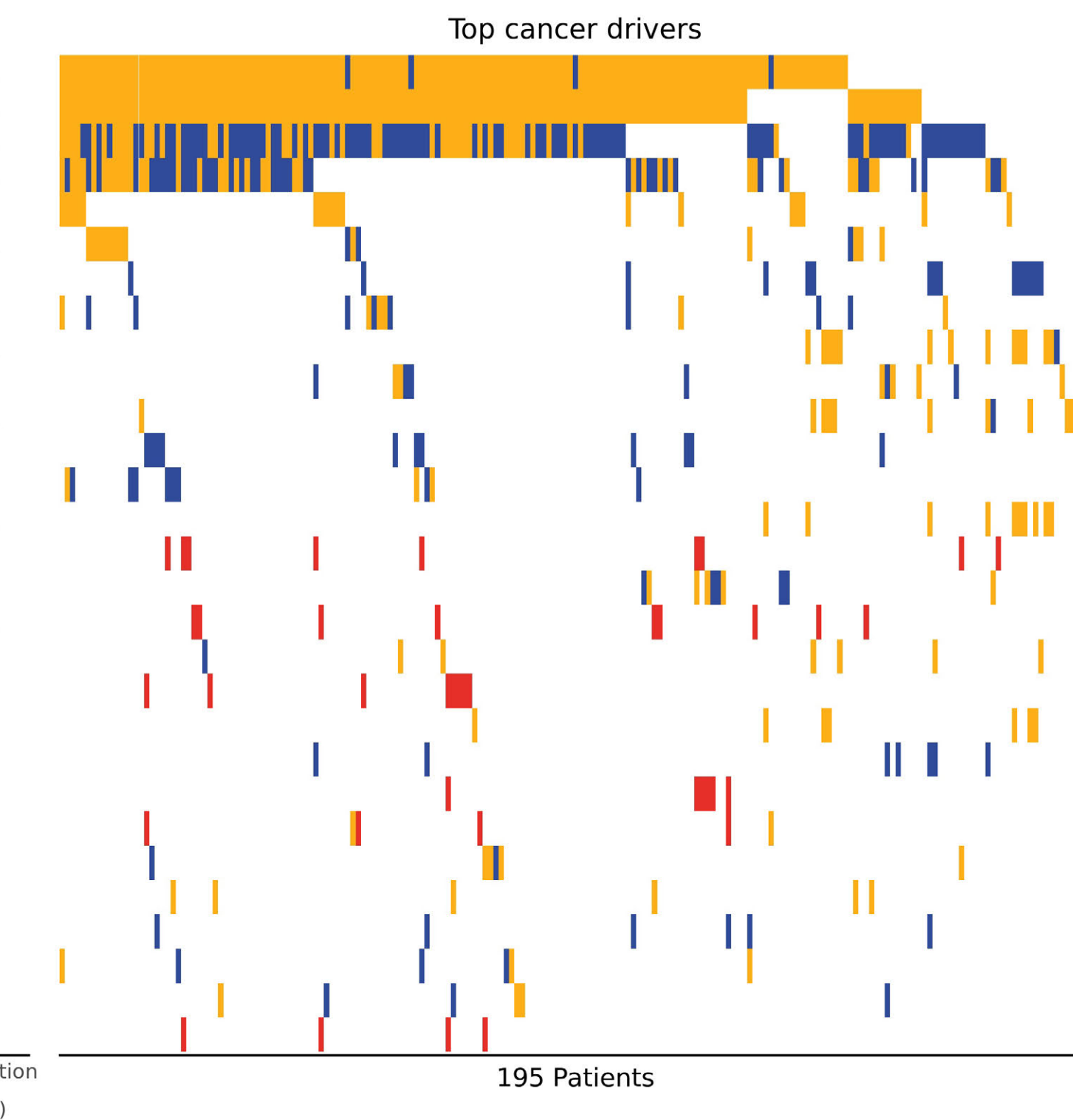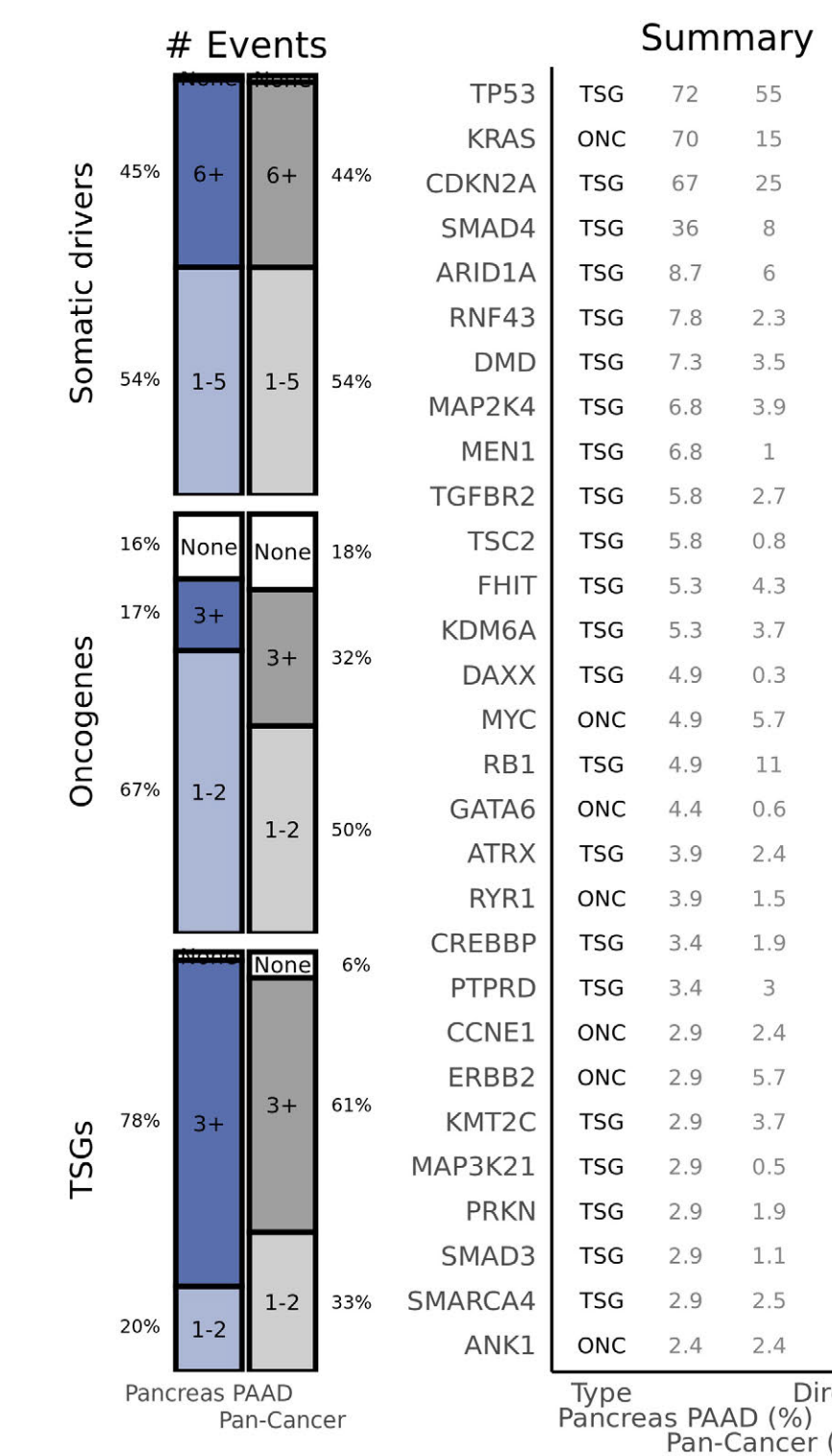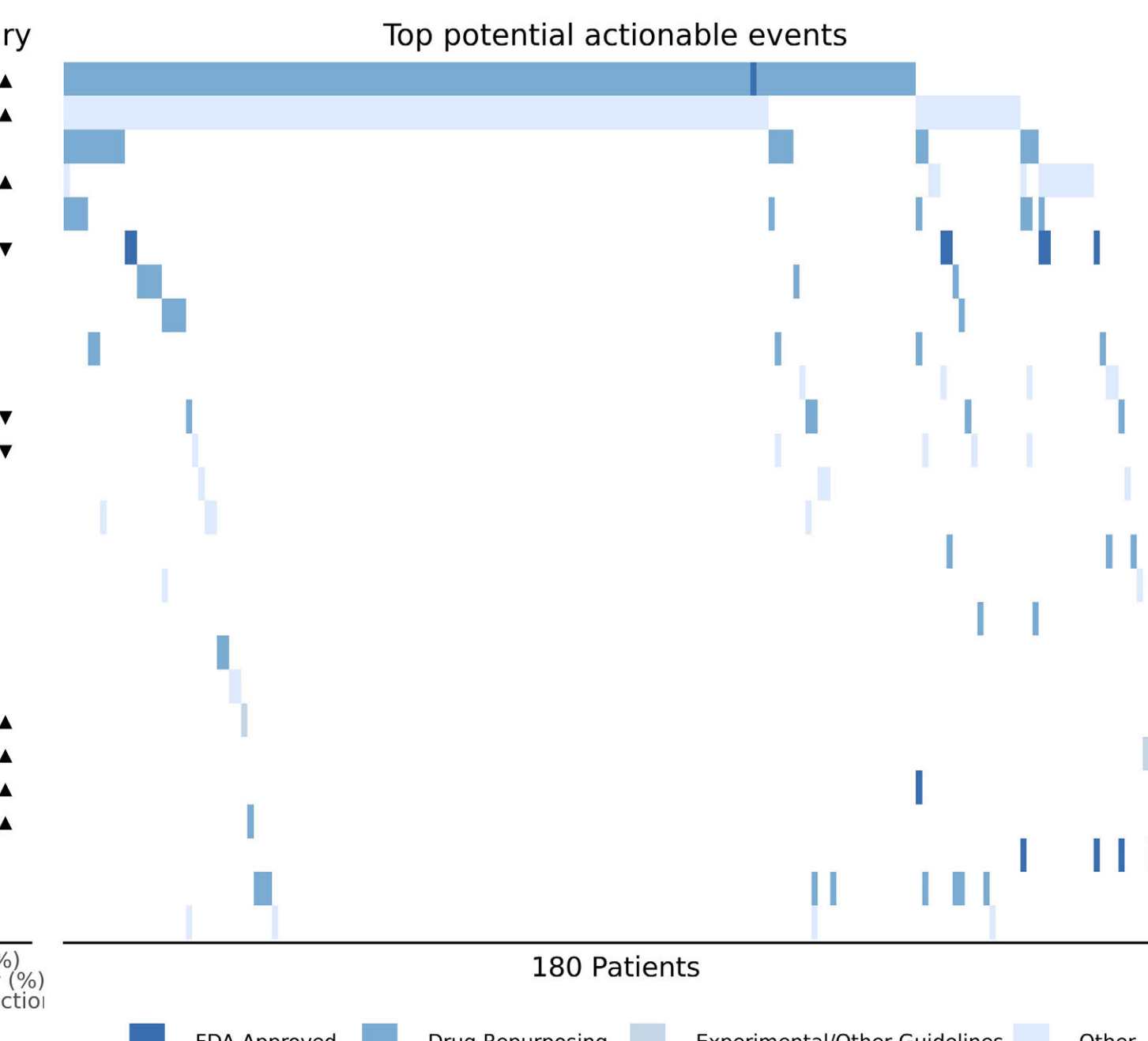** See documentation for further details on the WGS vs Panel coverage study.

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# The Genomic And Actionability Landscape Of Ovarian Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 246 |
| RNASeq | 137 |
| Age, Sex | 145 |
| Biopsy site | 140 |
| Pretreatment | 133 |
| Treatment | 119 → |
| Response | 105 → |

**Patients with treatment and response data**

Post-biopsy treatment / Responders

| | Treatment | Responders |
|---|---|---|
| Chemo | 61 | 30 (49%) |
| Multiple | 32 | 16 (50%) |
| Targeted | 5 | 1 (20%) |
| Hormonal | 9 | 1 (11%) |
| Immuno | 1 | 0 |
| Radio | 14 | 7 (50%) |
| Other | 1 | |
| None or NA | 0 | 0 |

## Processes Underlying Mutations

- DNA damage repair: 21%
- Chemical exposure: 18%
- Ageing: 12%
- APOBEC: 8%
- Tobacco: 2%
- UV light: 1%
- Unknown: 38%

Ovary — 246 Patients
Pan-Cancer — 6790 Patients

Ovary

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## Tumor Characteristics

Legend: Ovary / Pan-Cancer

| | Ovary | Pan-Cancer |
|---|---|---|
| TMB High | 3% | 21% |
| MSI High | 0% | 2% |
| WGD | 57% | 56% |
| Diploid Proportion | 35% | 34% |
| GIE HLA LOH | 19% | 19% |
| GIE Overall | 27% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 29% | 6% |

## Mutational Landscape

### Tumor purity
60% / 55%

### Clonal mutation fraction
91% / 95%

### Tumor mutational burden
2.9 / 4.2 — 3% High / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 7,712 | 983 / 669 / 183 | 270 | 96 / 92 |

Number of variants vs Quantile

### Telomere Length
0.76 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
7 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.081 / 0.15 — 0% Instable / 2%
MS indels per megabase

### Mean genome ploidy
2.7 / 2.6

### Aneuploidy Score
14 / 16

### % Copy number alteration
56% / 54%

### % Genome LOH
25% / 24%

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events (Somatic drivers / Oncogenes / TSGs)

| | Ovary | Pan-Cancer |
|---|---|---|
| Somatic drivers 6+ | 25% | 44% |
| Somatic drivers 1-5 | 70% | 54% |
| Somatic drivers None | 4% | |
| Oncogenes 3+ | 25% | 32% |
| Oncogenes 1-2 | 46% | 50% |
| Oncogenes None | 29% | 18% |
| TSGs 3+ | 42% | 61% |
| TSGs 1-2 | 47% | 33% |
| TSGs None | 11% | |

### Summary (Top cancer drivers)

| Gene | Type | Ovary (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 66 | 55 | ▲ |
| KRAS | ONC | 16 | 15 | |
| NF1 | TSG | 14 | 5 | ▲ |
| CDKN2A | TSG | 13 | 25 | ▼ |
| MYC | ONC | 9.3 | 5.7 | |
| RB1 | TSG | 9.3 | 11 | |
| CCNE1 | ONC | 8.5 | 2.4 | ▲ |
| PIK3CA | ONC | 7.3 | 13 | ▼ |
| ARID1A | TSG | 5.7 | 6 | |
| TG | ONC | 5.7 | 2.3 | |
| MAP2K4 | TSG | 5.3 | 3.9 | |
| PTEN | TSG | 5.3 | 14 | ▼ |
| RAD21 | ONC | 4.9 | 2.6 | |
| DMD | ONC | 4.5 | 3.5 | |
| TERT | ONC | 4.5 | 13 | ▼ |
| FOXL2 | ONC | 4.1 | 0.4 | ▲ |
| NF2 | TSG | 4.1 | 1.7 | |
| RYR1 | ONC | 4.1 | 1.5 | |
| BRAF | ONC | 3.7 | 6.2 | |
| CREBBP | TSG | 3.7 | 1.9 | |
| IKBKB | ONC | 3.7 | 1.9 | |
| MECOM | ONC | 3.7 | 0.8 | ▲ |
| OR4F21 | TSG | 3.7 | 2.4 | |
| KMT2D | TSG | 3.3 | 2.9 | |
| ANK1 | ONC | 2.8 | 2.4 | |
| CYLD | TSG | 2.8 | 1.9 | |
| ERBB2 | ONC | 2.8 | 5.7 | |
| MCL1 | ONC | 2.8 | 1.4 | |
| B2M | TSG | 2.4 | 1.9 | |

Top cancer drivers — 224 Patients

Legend: AMPLIFICATION / DELETION / MUTATION

## Potentially Actionable Events

### # Events (Actionable / Best treatment option)

| | Ovary | Pan-Cancer |
|---|---|---|
| Actionable 3+ | 10% | 26% |
| Actionable 1-2 | 63% | 56% |
| Actionable None | 27% | 18% |
| FDA | 33% | 36% |
| Off | 25% | 28% |
| Exp | 13% | 5% |
| Oth | 27% | 14% |
| None | | 18% |

### Summary (Top potential actionable events)

| Event | Ovary (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| HR deficiency | 28 | 5.8 | ▲ |
| KRAS | 15 | 14 | |
| CDKN2A | 12 | 24 | ▼ |
| BRCA1 | 8.9 | 1.3 | ▲ |
| PIK3CA | 7.3 | 13 | ▼ |
| PTEN | 5.3 | 13 | ▼ |
| BRCA2 | 4.1 | 2.4 | |
| NF2 | 4.1 | 1.6 | |
| BRAF | 3.3 | 5.9 | |
| KMT2D | 3.3 | 2.9 | |
| TMB High | 2.8 | 21 | ▼ |
| CHEK2 | 2.4 | 3 | |
| ERBB2 | 2.4 | 5.6 | |
| FGFR1 | 2 | 3.8 | |
| CDK12 | 1.6 | 0.9 | |
| NF1 | 1.6 | 0.4 | ▲ |
| ATM | 1.2 | 3.5 | |
| CCND1 | 1.2 | 5.3 | ▼ |
| CTNNB1 | 1.2 | 2.7 | |
| ERBB4 | 0.8 | 0.5 | |
| FGFR2 | 0.8 | 1.1 | |
| FGFR3 | 0.8 | 1.2 | |
| KDR | 0.8 | 0.1 | ▲ |
| Rest FDA | 0.4 | | |
| Rest Repurpose | 4.1 | | |
| Rest Experimental | 1.2 | | |
| Rest Other | 4.1 | | |

Top potential actionable events — 180 Patients

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

### # Events (Germline drivers)

| | Ovary | Pan-Cancer |
|---|---|---|
| 1+ | 23% | 16% |
| None | 77% | 84% |

### Summary (Top potential germline drivers)

| Gene | Type | Ovary (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRCA1 | TSG | 8.5 | 1.1 | ▲ |
| CHEK2 | TSG | 2.8 | 3.2 | |
| BRCA2 | TSG | 2.4 | 1.5 | |
| MUTYH | TSG | 2.4 | 1.9 | |
| SDHA | TSG | 1.6 | 0.5 | |
| RAD50 | TSG | 1.2 | 0.5 | |
| SMARCA4 | TSG | 1.2 | 0.1 | ▲ |
| POLD1 | TSG | 0.8 | 0.1 | ▲ |
| RAD51B | TSG | 0.8 | 0.1 | ▲ |

Top potential germline drivers — 51 Patients

Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other / None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Exp/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 80 | 63 | 28 | 19 | 56 |
| Comprehensive 521 gene panel | 41 | 58 | 27 | 27 | 93 |
| Targeted 50 gene panel | 50 | 10 | 20 | | 160 |

# of patients in Hartwig database

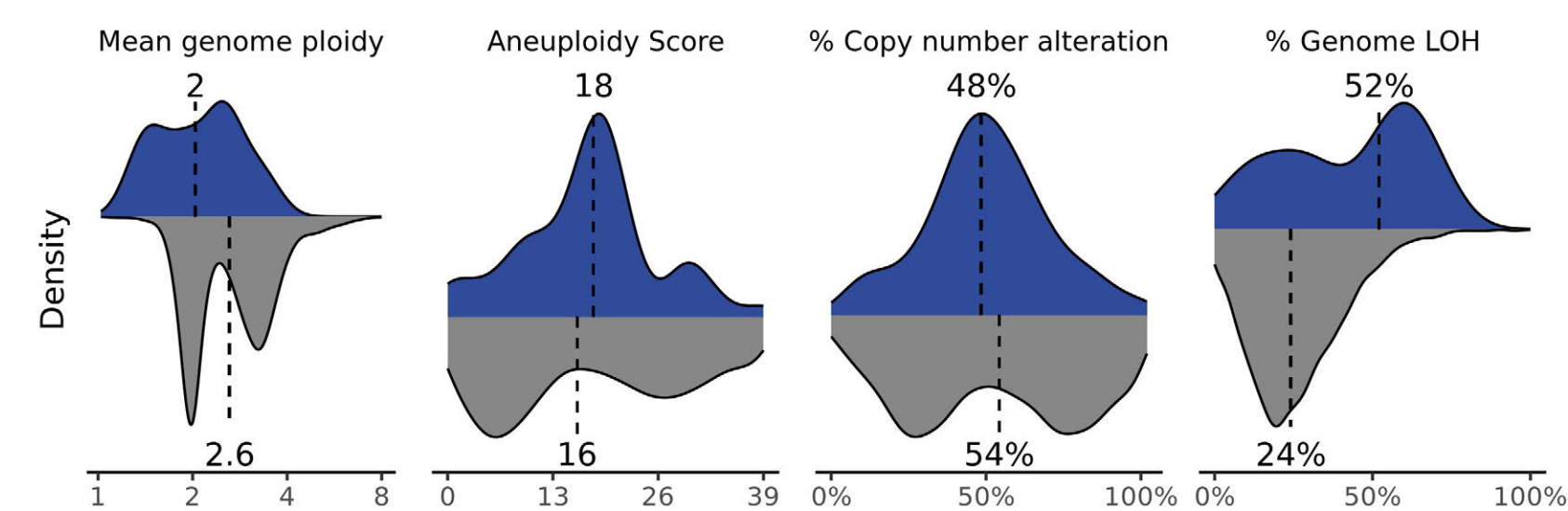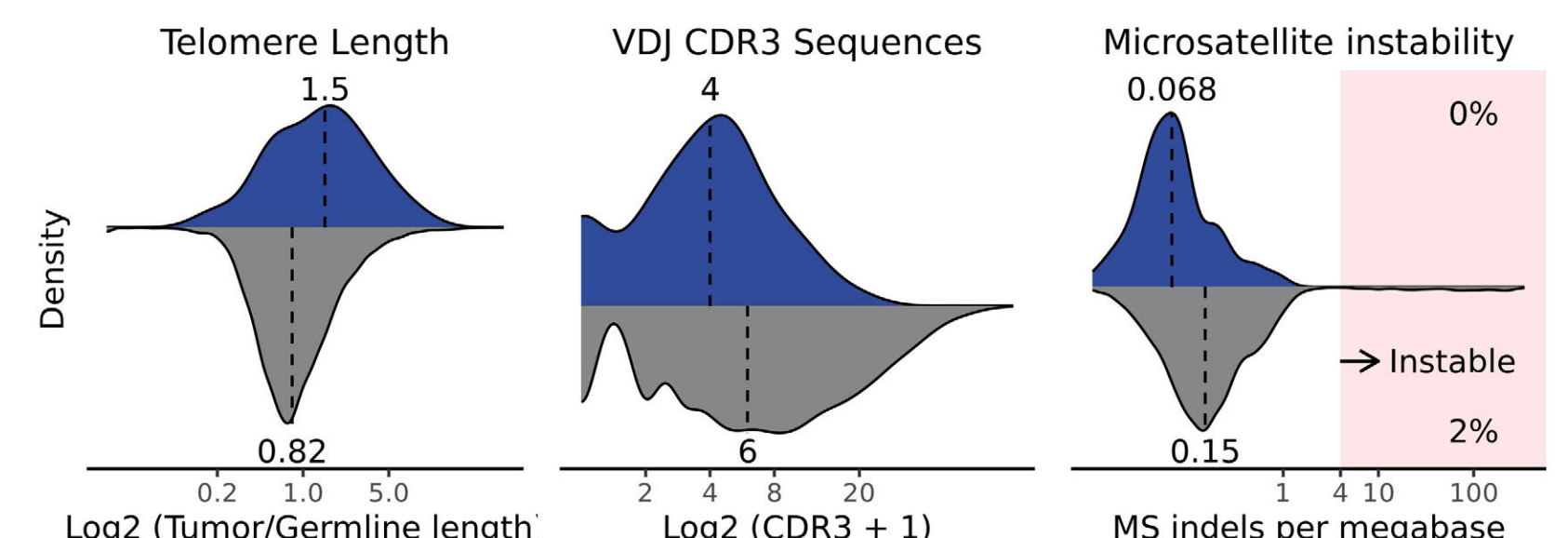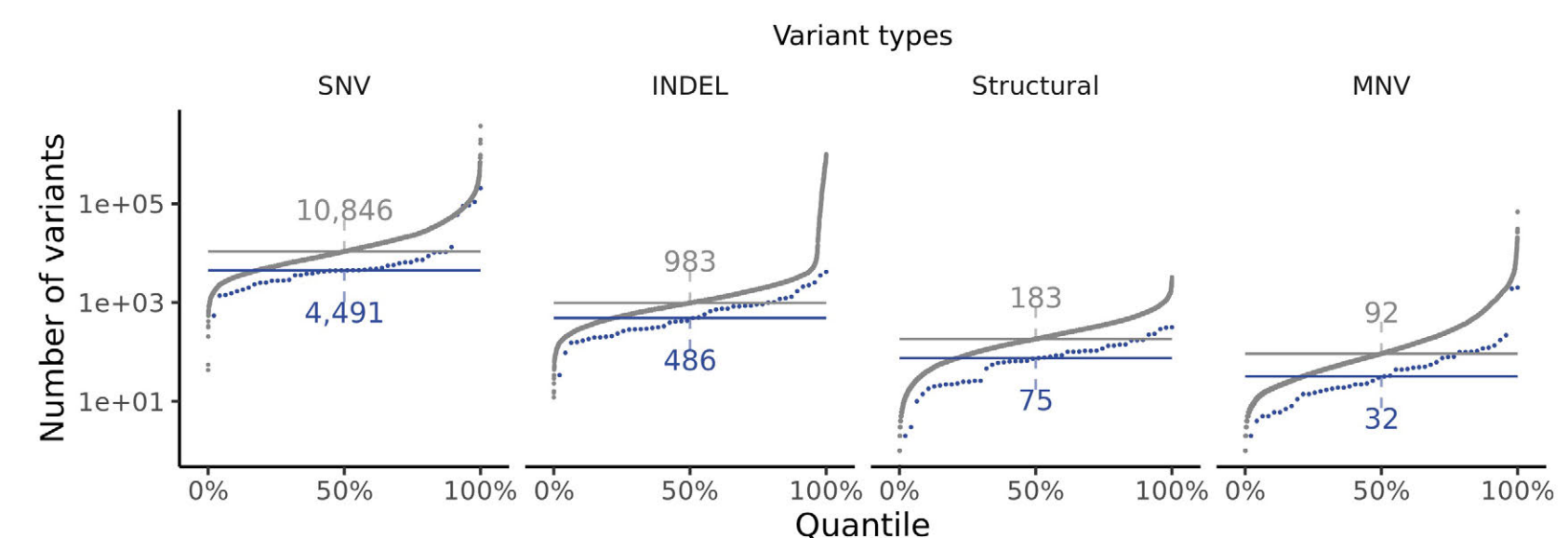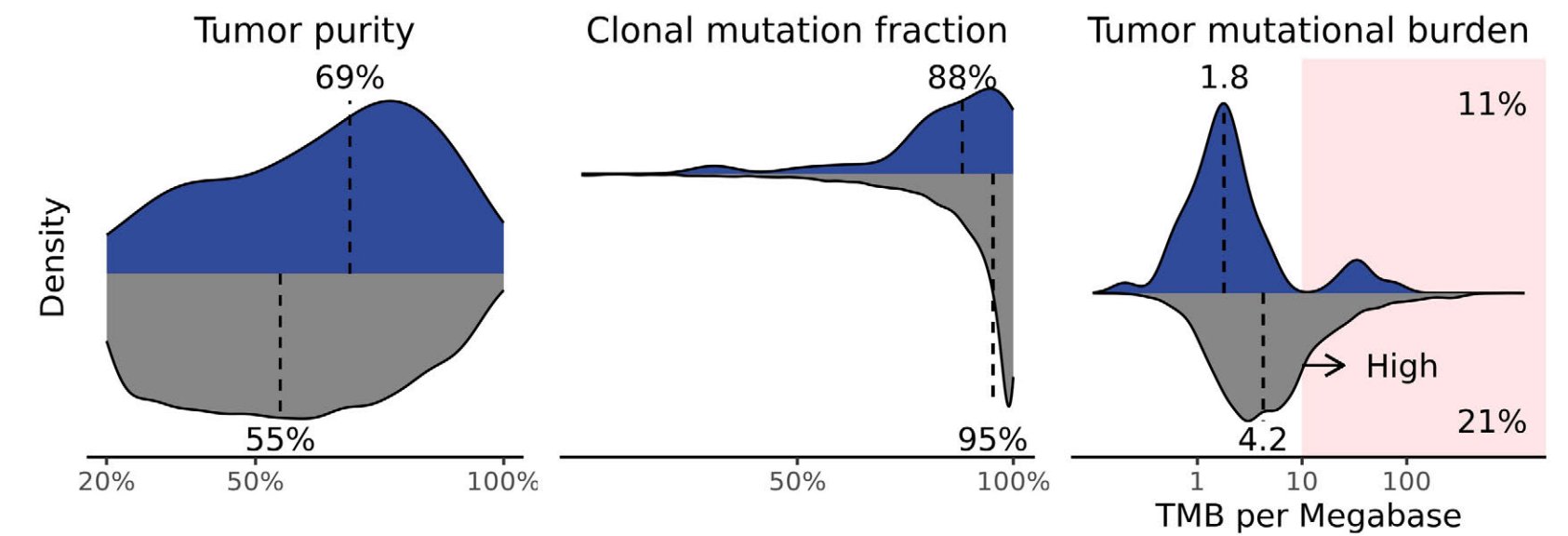### Average number of identified potentially actionable events identified by test strategy

| | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.49 | 0.35 | 0.32 | 0.39 | 1.5 |
| Comprehensive 521 gene panel | 0.29 | 0.31 | | | 1 |
| Targeted 50 gene panel | 0.23 | | | | 0.5 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
- HRD: 70
- Partial CN Loss: 1

Drug Repurposing:
- Fusion: 7
- Partial CN Loss: 6
- HMZ Disruption: 1

Experimental/Other Guidelines:
- Partial CN Loss: 31
- HMZ Disruption: 2
- Fusion: 1
- Small Variant: 1
- Full CN Gain: 1

Other:
- Partial CN Loss: 12
- Full CN Loss: 5
- Small Variant: 1
- HMZ Disruption: 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved:
- HRD: 70
- Small Variant: 32
- TMB High: 7
- Splice Site: 3
- Partial CN Loss: 1

Drug Repurposing:
- Small Variant: 14
- Fusion: 7
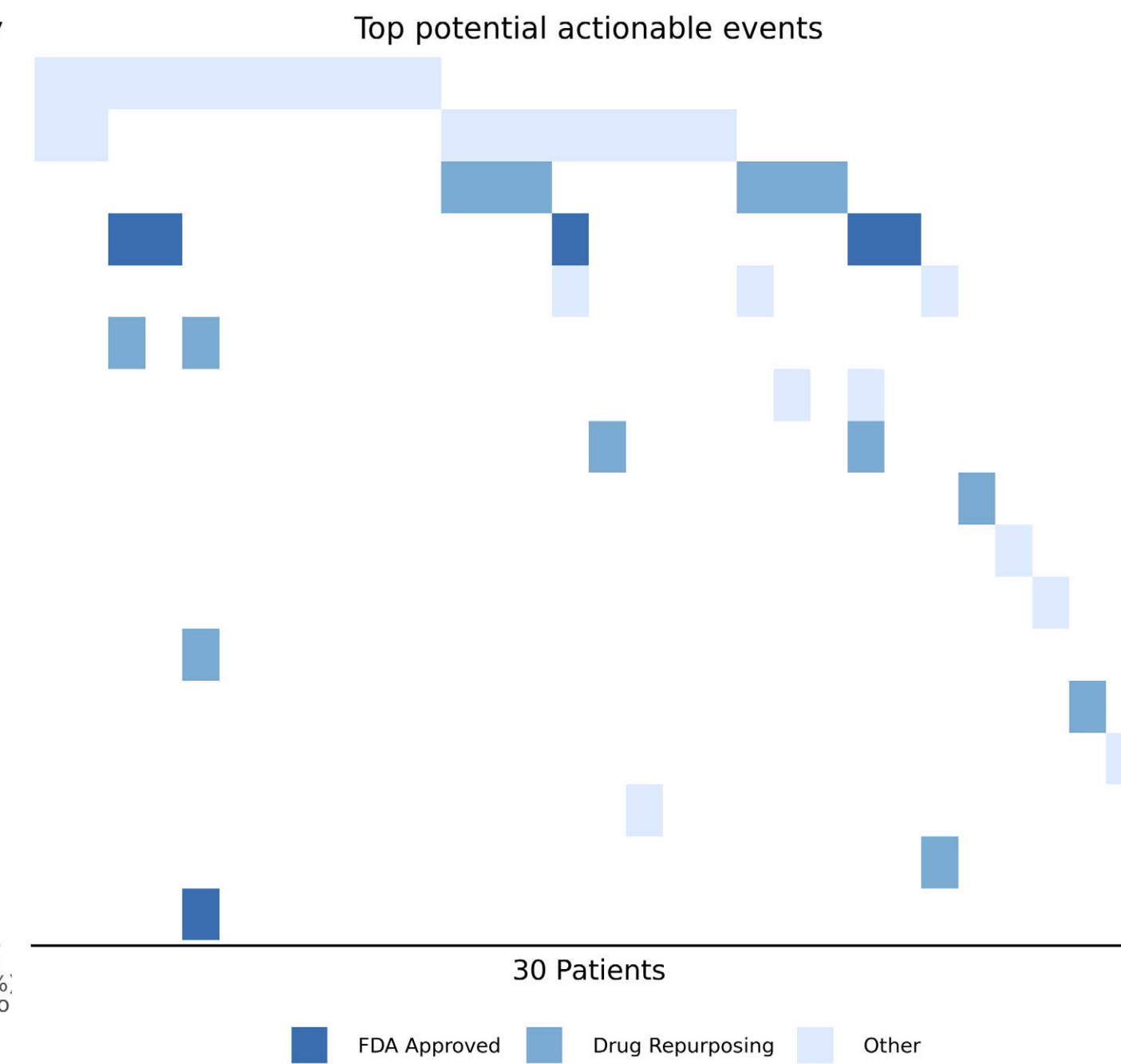- Partial CN Loss: 6
- Splice Site: 2
- HMZ Disruption: 1

Experimental/Other Guidelines:
- Partial CN Loss: 31
- Full CN Gain: 27
- Full CN Loss: 5
- HMZ Disruption: 2
- Fusion: 1

Other:
- Small Variant: 29
- Partial CN Loss: 12
- Full CN Loss: 9
- Splice Site: 3
- Full CN Gain: 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Pancreatic Carcinoma

## Cohort Metadata

### Data availability
Number of patients with data

| | |
|---|---|
| WGS | 206 |
| RNASeq | 149 |
| Age, Sex | 168 |
| Biopsy site | 166 |
| Pretreatment | 166 |
| Treatment | 150 |
| Response | 117 |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | | |
|---|---|---|
| Chemo | 45 | 12 (27%) |
| Multiple | 57 | 23 (40%) |
| Targeted | 9 | 1 (11%) |
| Hormonal | 5 | 0 |
| Immuno | 1 | 0 |
| Radio | 6 | 0 |
| Other | 2 | 0 |
| None or NA | 0 | |

## Tumor Characteristics

Pancreas PAAD / Pan-Cancer

| | Pancreas PAAD | Pan-Cancer |
|---|---|---|
| TMB High | 3% | 21% |
| MSI High | 0% | 2% |
| WGD | 51% | 56% |
| Diploid Proportion | 34% | 34% |
| GIE HLA LOH | 28% | 19% |
| GIE Overall | 31% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 9% | 6% |

## Mutational Landscape

### Tumor purity
43% / 55%

### Clonal mutation fraction
96% / 95%

### Tumor mutational burden
2.3 / 4.2 — High 3% / 21%

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Pancreas PAAD | 5,730 | 749 | 106 | 37 |

### Telomere Length
0.76 / 0.82

### VDJ CDR3 Sequences
6 / 6

### Microsatellite instability
0.15 / 0.15 — Instable 0% / 2%

### Mean genome ploidy
2.4 / 2.6

### Aneuploidy Score
18 / 16

### % Copy number alteration
54% / 54%

### % Genome LOH
28% / 24%

## Processes Underlying Mutations

- DNA damage repair: 25%
- Ageing: 18%
- Chemical exposure: 16%
- APOBEC: 4%
- UV light: 4%
- Tobacco: 2%
- Unknown: 31%

Pancreas PAAD — 206 Patients
Pan-Cancer — 6790 Patients

Pancreas

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary

Somatic drivers: 45% 6+ / 6+ ; 54% 1-5 / 1-5 (Pan-Cancer 44% / 18%)

| Gene | Type | Pancreas PAAD % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| TP53 | TSG | 72 | 55 | ▲ |
| KRAS | ONC | 70 | 15 | ▲ |
| CDKN2A | TSG | 67 | 25 | ▲ |
| SMAD4 | TSG | 36 | 8 | ▲ |
| ARID1A | TSG | 8.7 | 6 | |
| RNF43 | TSG | 7.8 | 2.3 | ▲ |
| DMD | TSG | 7.3 | 3.5 | |
| MAP2K4 | TSG | 6.8 | 3.9 | |
| MEN1 | TSG | 6.8 | 1.9 | |
| TGFBR2 | TSG | 5.8 | 2.7 | |
| TSC2 | TSG | 5.3 | 3.7 | |
| FHIT | TSG | 5.3 | 4.3 | |
| KDM6A | TSG | 5.3 | 3.7 | |
| DAXX | TSG | 4.9 | 0.3 | ▲ |
| MYC | ONC | 4.9 | 5.3 | ▲ |
| RB1 | ONC | 4.9 | 11 | ▼ |
| GATA6 | ONC | 4.4 | 0.6 | ▲ |
| ATRX | ONC | 3.9 | 2.4 | |
| RYR1 | ONC | 3.9 | 1.5 | |
| CREBBP | TSG | 3.4 | 1.9 | |
| PTPRD | TSG | 3.4 | 3 | |
| CCNE1 | ONC | 2.9 | 1.5 | |
| ERBB2 | ONC | 2.9 | 5.7 | |
| KMT2C | TSG | 2.9 | 3.7 | |
| MAP3K21 | TSG | 2.9 | 1.9 | |
| PRKN | TSG | 2.9 | 1.1 | |
| SMAD3 | TSG | 2.9 | 2.5 | |
| SMARCA4 | TSG | 2.9 | 2.5 | |
| ANK1 | ONC | 2.4 | 2.4 | |

Oncogenes: 16% None / None (18%); 17% 3+ / 3+ (32%); 67% 1-2 / 1-2 (50%)
TSGs: 78% 3+ / 3+ (61%); 20% 1-2 / 1-2 (33%)

Top cancer drivers — 195 Patients
Legend: AMPLIFICATION / DELETION / MUTATION

## Potentially Actionable Events

### # Events / Summary

Actionable: 13% None / None (18%); 23% 3+ / 3+ (26%); 64% 1-2 / 1-2 (56%)

| Event | Pancreas PAAD % | Pan-Cancer % | Direction |
|---|---|---|---|
| KRAS | 67 | 14 | ▲ |
| CDKN2A | 64 | 24 | ▲ |
| HR deficiency | 9.2 | 5.8 | |
| TSC2 | 6.3 | 0.8 | ▲ |
| BRCA2 | 4.4 | 2.4 | |
| TMB High | 3.4 | 21 | ▼ |
| ERBB2 | 2.9 | 5.6 | |
| ATM | 2.4 | 3.5 | |
| BRCA1 | 2.4 | 1.3 | |
| CTNNB1 | 2.4 | 2.7 | |
| PIK3CA | 2.4 | 13 | ▼ |
| PTEN | 2.4 | 13 | ▼ |
| FGFR1 | 1.9 | 3.8 | |
| KMT2D | 1.9 | 2.9 | |
| NRAS | 1.5 | 2.6 | |
| CDK4 | 1 | 1.9 | |
| MAP2K1 | 1 | 0.8 | |
| MET | 1 | 1.7 | |
| VEGFA | 1 | 0.7 | |
| ANK1 – NRG1 fusion | 0.5 | 0 | ▲ |
| ATP1B1 – NRG1 fusion | 0.5 | 0 | ▲ |
| ATP1B1 – NTRK1 fusion | 0.5 | 0 | ▲ |
| CHEK1 | 0.5 | 0.1 | ▲ |
| Rest FDA | 1.9 | | |
| Rest Repurpose | 4.9 | | |
| Rest Other | 2.4 | | |

Best treatment option: 13% None / None (18%); 9% Oth (14%); Exp 5%; 72% Off (28%); 6% FDA (36%)

Top potential actionable events — 180 Patients
Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

Germline drivers: 79% None / None (84%); 21% 1+ / 1+ (16%)

| Gene | Type | Pancreas PAAD % | Pan-Cancer % | Direction |
|---|---|---|---|---|
| MUTYH | TSG | 2.9 | 1.9 | |
| BRCA2 | TSG | 2.4 | 1.5 | |
| RAD50 | TSG | 1.9 | 0.5 | ▲ |
| BRCA1 | TSG | 1.5 | 1.1 | |
| CHEK2 | TSG | 1.5 | 3.2 | |
| MSH2 | TSG | 1.5 | 1 | |
| POLE | TSG | 1.5 | 0.2 | ▲ |
| ATM | TSG | 1 | 1 | |
| CHEK1 | TSG | 1 | 0.1 | ▲ |

Top potential germline drivers — 30 Patients
Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other / None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA Approved | Other | | | |
|---|---|---|---|---|---|
| WGS | 12 | 148 | 10 | 12 | 24 |
| Comprehensive 521 gene panel | 8 | 150 | 7 | 10 | 31 |
| Targeted 50 gene panel | | 144 | 9 | | 48 |

(# of patients in Hartwig database)

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | Total |
|---|---|---|---|---|
| WGS | 1 | 0.6 | 0.54 | 2.3 |
| Comprehensive 521 gene panel | 0.89 | 0.45 | 0.51 | 1.9 |
| Targeted 50 gene panel | 0.75 | 0.36 | 0.26 | 1.4 |

(Average number of actionable events per patient)

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: Fusion 4
Drug Repurposing: HRD 19; Fusion 5; Partial CN Loss 5; HMZ Disruption 1; Splice Site 1
Experimental/Other Guidelines: Partial CN Loss 23; Full CN Loss 6; Fusion 2
Other: Partial CN Loss 5; HMZ Disruption 2

(Number of Missed Events)

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 7; Fusion 4
Drug Repurposing: Small Variant 22; HRD 19; Splice Site 9; Fusion 5; Partial CN Loss 5
Experimental/Other Guidelines: Partial CN Loss 23; Full CN Gain 17; Full CN Loss 7; Fusion 2; Partial CN Gain 1
Other: Small Variant 44; Partial CN Loss 5; Splice Site 5; Full CN Gain 2; HMZ Disruption 2

(Number of Missed Events)

# The Genomic And Actionability Landscape Of Pancreatic Neuroendocrine

## Cohort Metadata

### Data availability
Number of patients with data

- WGS: 47
- RNASeq: 25
- Age, Sex: 34
- Biopsy site: 33
- Pretreatment: 33
- Treatment: 31 →
- Response: 24 →

### Patients with treatment and response data

Post-biopsy treatment / Responders

- Chemo: 12 / 2 (17%)
- Multiple: 0 / 0
- Targeted: 6 / 0
- Hormonal: 5 / 0
- Immuno: 0 / 0
- Radio: 3 / 0
- Other: 2 / 0
- None or NA: 0 / 0

## Tumor Characteristics

Legend: Pancreas PANET / Pan-Cancer

| | PANET | Pan-Cancer |
|---|---|---|
| TMB High | 11% | 21% |
| MSI High | 0% | 2% |
| WGD | 45% | 56% |
| Diploid Proportion | 34% | 34% |
| GIE HLA LOH | 55% | 19% |
| GIE Overall | 57% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 2% | 6% |

## Mutational Landscape

### Tumor purity
69% / 55%

### Clonal mutation fraction
88% / 95%

### Tumor mutational burden
1.8 / 4.2 — High 11% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| PANET | 4,491 | 486 | 75 | 32 |

Number of variants vs Quantile

### Telomere Length
1.5 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
4 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.068 / 0.15 — Instable 0% / 2%
MS indels per megabase

### Mean genome ploidy
2 / 2.6

### Aneuploidy Score
18 / 16

### % Copy number alteration
48% / 54%

### % Genome LOH
52% / 24%

## Processes Underlying Mutations

- Chemical exposure: 42%
- Tobacco: 13%
- UV light: 6%
- DNA damage repair: 5%
- Ageing: 5%
- APOBEC: 4%
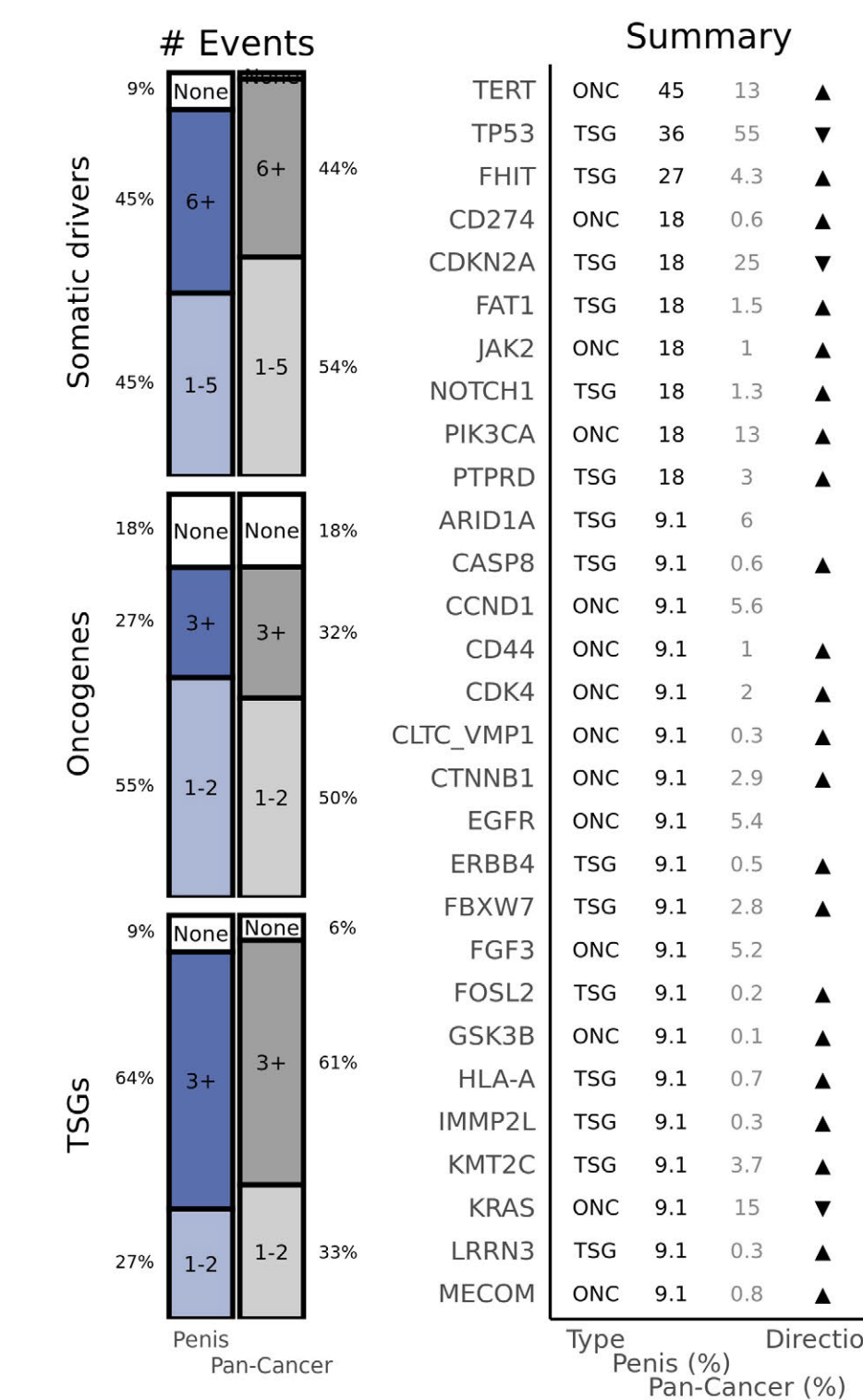- Unknown: 25%
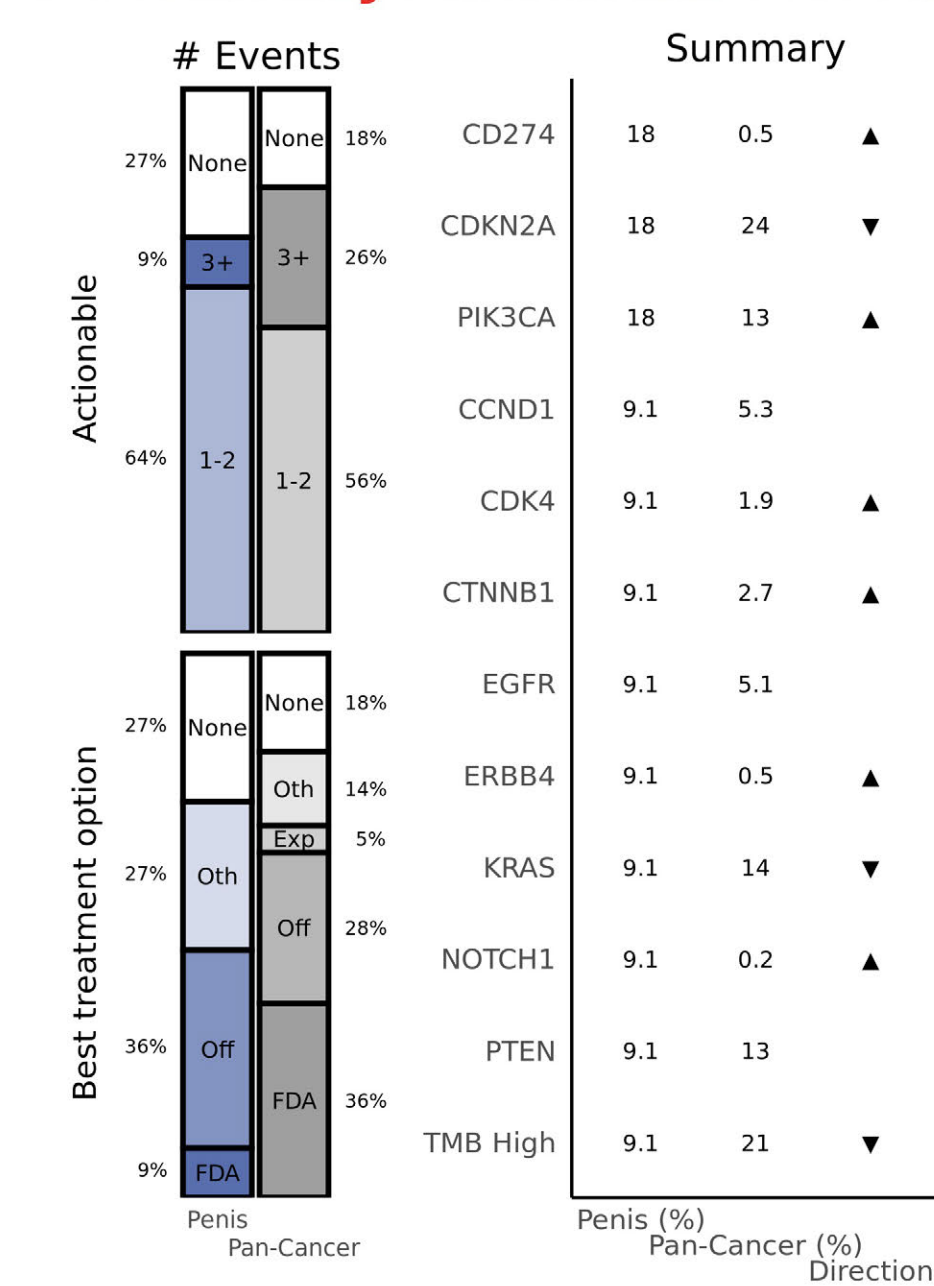
Pancreas PANET — 47 Patients
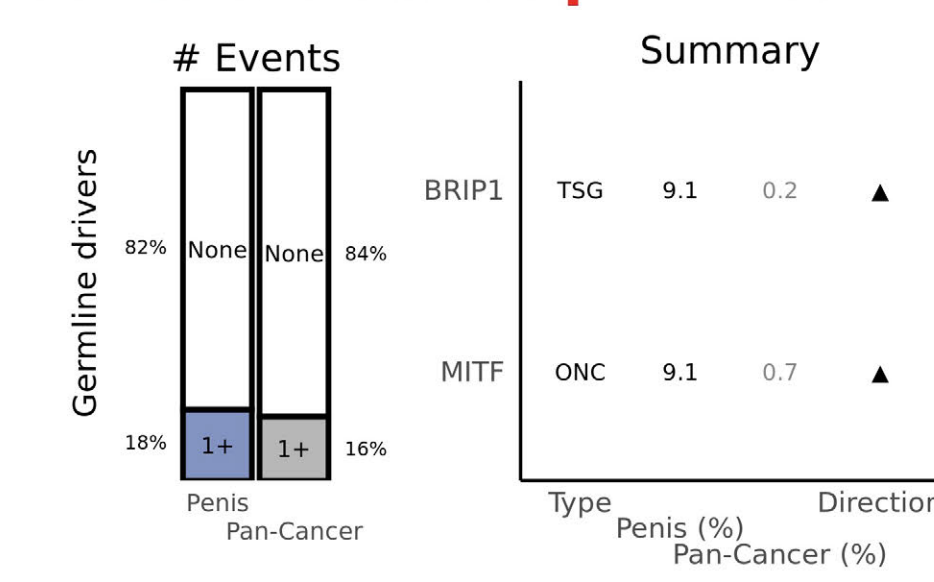Pan-Cancer — 6790 Patients

Pancreas

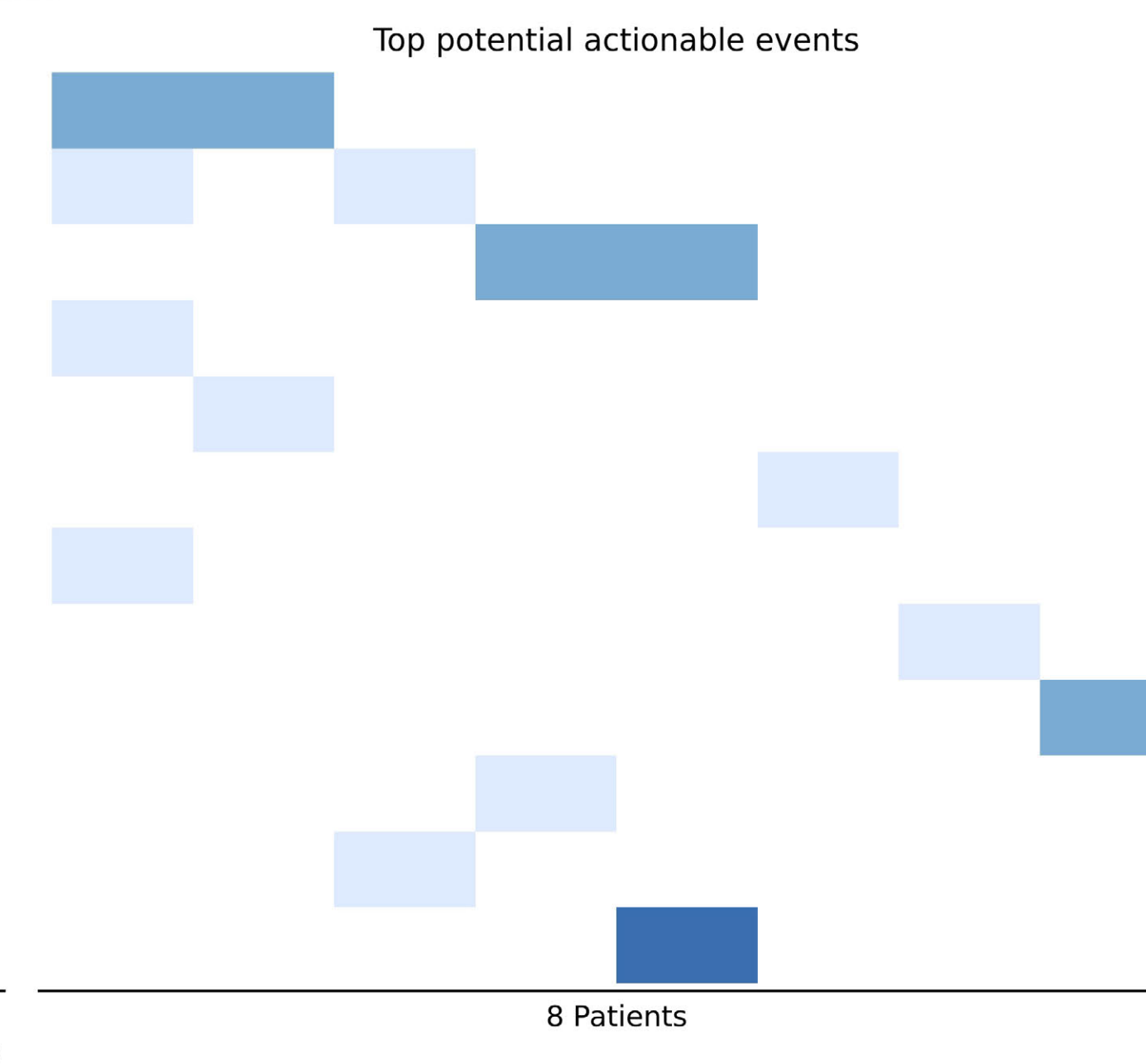## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

Somatic drivers: 23% 6+ / 44% 6+ ; 74% 1-5 / 54% 1-5
Oncogenes: 57% 3+ / 18% None, 32% 3+ ; 4% None, 38% 1-2 / 50% 1-2
TSGs: 68% 3+ / 4% None, 61% 3+ ; 28% 1-2 / 33% 1-2

| Gene | Type | Pancreas PANET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MEN1 | TSG | 32 | 1 | ▲ |
| TP53 | TSG | 32 | 55 | ▼ |
| CDKN2A | TSG | 26 | 25 | |
| DMD | TSG | 26 | 3.5 | ▲ |
| DAXX | TSG | 23 | 0.3 | ▲ |
| TSC2 | TSG | 23 | 0.8 | ▲ |
| CREBBP | TSG | 13 | 1.9 | ▲ |
| KRAS | ONC | 13 | 15 | |
| RB1 | TSG | 13 | 11 | |
| ATRX | TSG | 11 | 2.4 | ▲ |
| SETD2 | TSG | 11 | 2.1 | ▲ |
| PTPRD | TSG | 8.5 | 3 | ▲ |
| CTNNB1 | ONC | 6.4 | 2.9 | |
| MAP2K4 | TSG | 6.4 | 3.9 | |
| MGA | TSG | 6.4 | 1.5 | ▲ |
| PBRM1 | TSG | 6.4 | 3.2 | |
| SMAD4 | TSG | 6.4 | 8 | |
| ARID1A | TSG | 4.3 | 6 | |
| AXIN1 | TSG | 4.3 | 0.6 | ▲ |
| BCOR | TSG | 4.3 | 0.7 | ▲ |
| CDKN1A | TSG | 4.3 | 0.4 | ▲ |
| DEPDC5 | TSG | 4.3 | 0.4 | ▲ |
| KMT2D | TSG | 4.3 | 2.9 | |
| LINC00290 | TSG | 4.3 | 0.9 | ▲ |
| NRAS | ONC | 4.3 | 2.8 | |
| PIK3CA | ONC | 4.3 | 13 | ▼ |
| PRKN | TSG | 4.3 | 1.9 | |
| ACVR2A | TSG | 2.1 | 2 | |
| AR | ONC | 2.1 | 5.6 | |

Top cancer drivers — 44 Patients
Legend: DELETION / MUTATION

## Potentially Actionable Events

### # Events / Summary

Actionable: 36% None / 18% None, 26% 3+ ; 9% 3+ / 55% 1-2 / 56% 1-2
Best treatment option: 36% None / 18% None, 14% Oth, 5% Exp ; 30% Oth / 28% Off ; 21% Off / 13% FDA / 36% FDA

| Gene | Pancreas PANET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| TSC2 | 23 | 0.8 | ▲ |
| CDKN2A | 21 | 24 | |
| KRAS | 13 | 14 | |
| TMB High | 11 | 21 | ▼ |
| CTNNB1 | 6.4 | 2.7 | |
| BRCA2 | 4.3 | 2.4 | |
| KMT2D | 4.3 | 2.9 | |
| PIK3CA | 4.3 | 13 | ▼ |
| BRCA1 | 2.1 | 1.3 | |
| CDK4 | 2.1 | 1.9 | |
| FGFR1 | 2.1 | 3.8 | |
| HR deficiency | 2.1 | 5.8 | |
| HRAS | 2.1 | 0.6 | ▲ |
| KDM5C | 2.1 | 0.6 | ▲ |
| MTOR | 2.1 | 0.6 | ▲ |
| NRAS | 2.1 | 2.6 | |
| SH2D2A - NTRK1 fusion | 2.1 | 0 | |

Top potential actionable events — 30 Patients
Legend: FDA Approved / Drug Repurposing / Other

## Germline Predisposition

### # Events / Summary

Germline drivers: 81% None / 84% None ; 19% 1+ / 16% 1+

| Gene | Type | Pancreas PANET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| RAD50 | TSG | 4.3 | 0.5 | ▲ |
| TP53 | TSG | 4.3 | 0.5 | ▲ |
| ATM | TSG | 2.1 | 1 | |
| BRCA1 | TSG | 2.1 | 1.1 | |
| BRCA2 | TSG | 2.1 | 1.5 | |
| MSH2 | TSG | 2.1 | 1 | |
| MUTYH | TSG | 2.1 | 1.9 | |
| POLE | TSG | 2.1 | 0.2 | ▲ |

Top potential germline drivers — 9 Patients
Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Other / Experimental/Other Guidelines / None

### Highest evidence level treatment option identified by test strategy

| Test | FDA Approved | Drug Repurposing | Other | Experimental/Other | None |
|---|---|---|---|---|---|
| WGS | 6 | 10 | 6 | 9 | 16 |
| Comprehensive 521 gene panel | 5 | 11 | 6 | 7 | 18 |
| Targeted 50 gene panel | 10 | 6 | | | 31 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test | | | | Total |
|---|---|---|---|---|
| WGS | 0.32 | 0.28 | 0.43 | 1.1 |
| Comprehensive 521 gene panel | 0.26 | 0.21 | 0.38 | 1 |
| Targeted 50 gene panel | 0.21 | | | 0.5 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: Fusion 1
Drug Repurposing: Partial CN Loss 1, HRD 1, Splice Site 1
Experimental/Other Guidelines: Partial CN Loss 2, Full CN Loss 1
Other: Partial CN Loss 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 5, Fusion 1
Drug Repurposing: Splice Site 3, Partial CN Loss 1, HRD 1
Experimental/Other Guidelines: Partial CN Loss 2, Full CN Gain 1, Full CN Loss 1
Other: Small Variant 11, Splice Site 4, Partial CN Loss 2

Number of Missed Events

# The Genomic And Actionability Landscape Of Penile Cancer

## Cohort Metadata

### Data availability

Number of patients with data — WGS 11, RNASeq 5, Age, Sex 5, Biopsy site 3, Pretreatment 5, Treatment 2, Response 2

### Patients with treatment and response data

Post-biopsy treatment / Responders:
Chemo 1 / 0, Multiple 0 / 0, Targeted 0 / 0, Hormonal 0 / 0, Immuno 2 / 1 (50%), Radio 1 / 1 (100%), Other 0 / 0, None or NA 0 / 0

## Tumor Characteristics

Penis / Pan-Cancer:
TMB High 9% / 21%, MSI High 0% / 2%, WGD 36% / 56%, Diploid Proportion 43% / 34%, GIE HLA LOH 18% / 19%, GIE Overall 55% / 26%, Viral Insertions 55% / 3%, HRD 0% / 6%

## Mutational Landscape

### Tumor purity
62% / 55%

### Clonal mutation fraction
93% / 95%

### Tumor mutational burden
3.8 / 4.2 — High 9% / 21%, TMB per Megabase

### Variant types
Number of variants:
- SNV: 10,846 / 10,144
- INDEL: 983 / 858
- Structural: 183 / 150
- MNV: 92 / 88

### Telomere Length
1.1 / 0.82 — Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
11 / 6 — Log2 (CDR3 + 1)

### Microsatellite instability
0.11 / 0.15 — Instable 0% / 2%, MS indels per megabase

### Mean genome ploidy
2.2 / 2.6

### Aneuploidy Score
11 / 16

### % Copy number alteration
35% / 54%

### % Genome LOH
24% / 24%

## Processes Underlying Mutations

- APOBEC: 53%
- Chemical exposure: 13%
- DNA damage repair: 8%
- Ageing: 7%
- UV light: 3%
- Tobacco: 2%
- Unknown: 15%

Penis 11 Patients / Pan-Cancer 6790 Patients

Penis



Made with bioRender
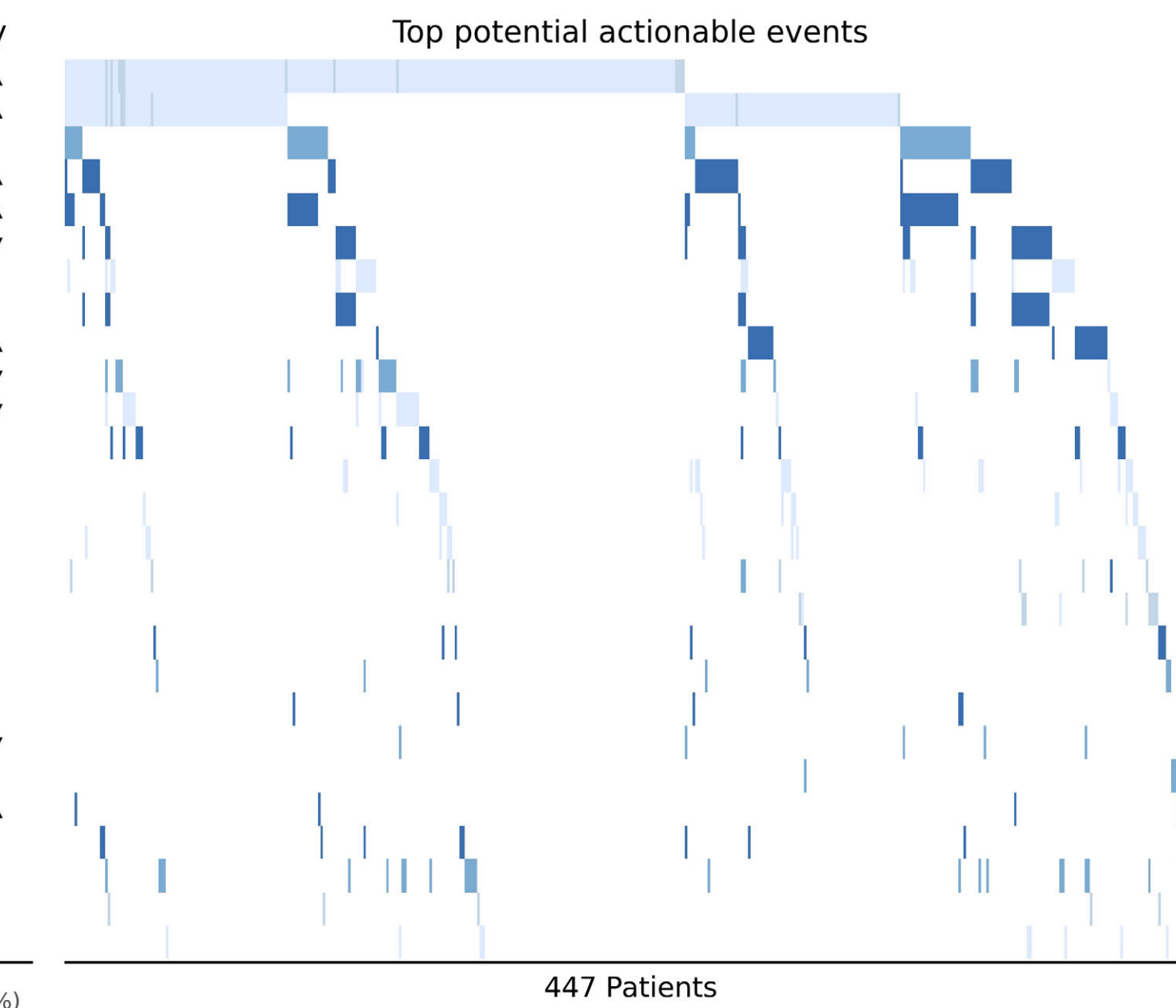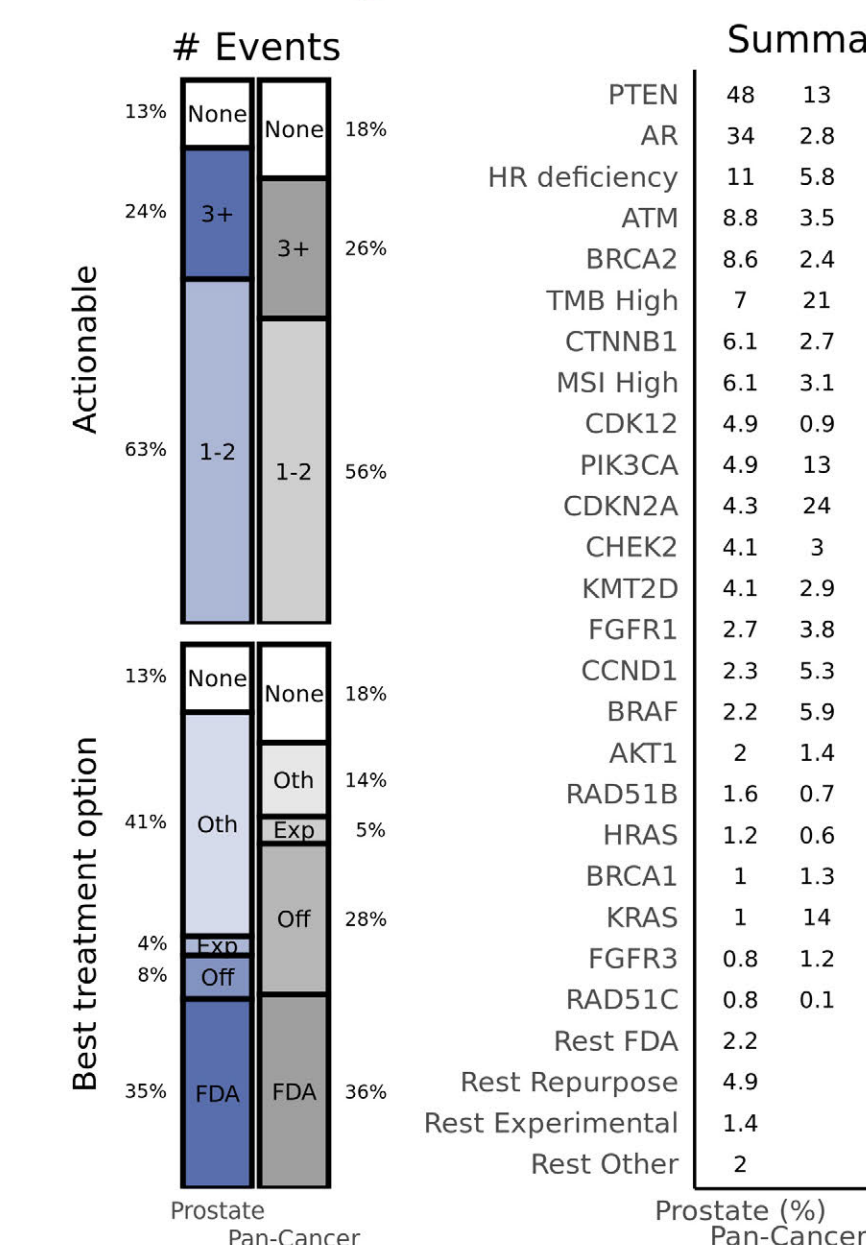
## Copy Number Alteration Profile



## Cancer Driver Landscape

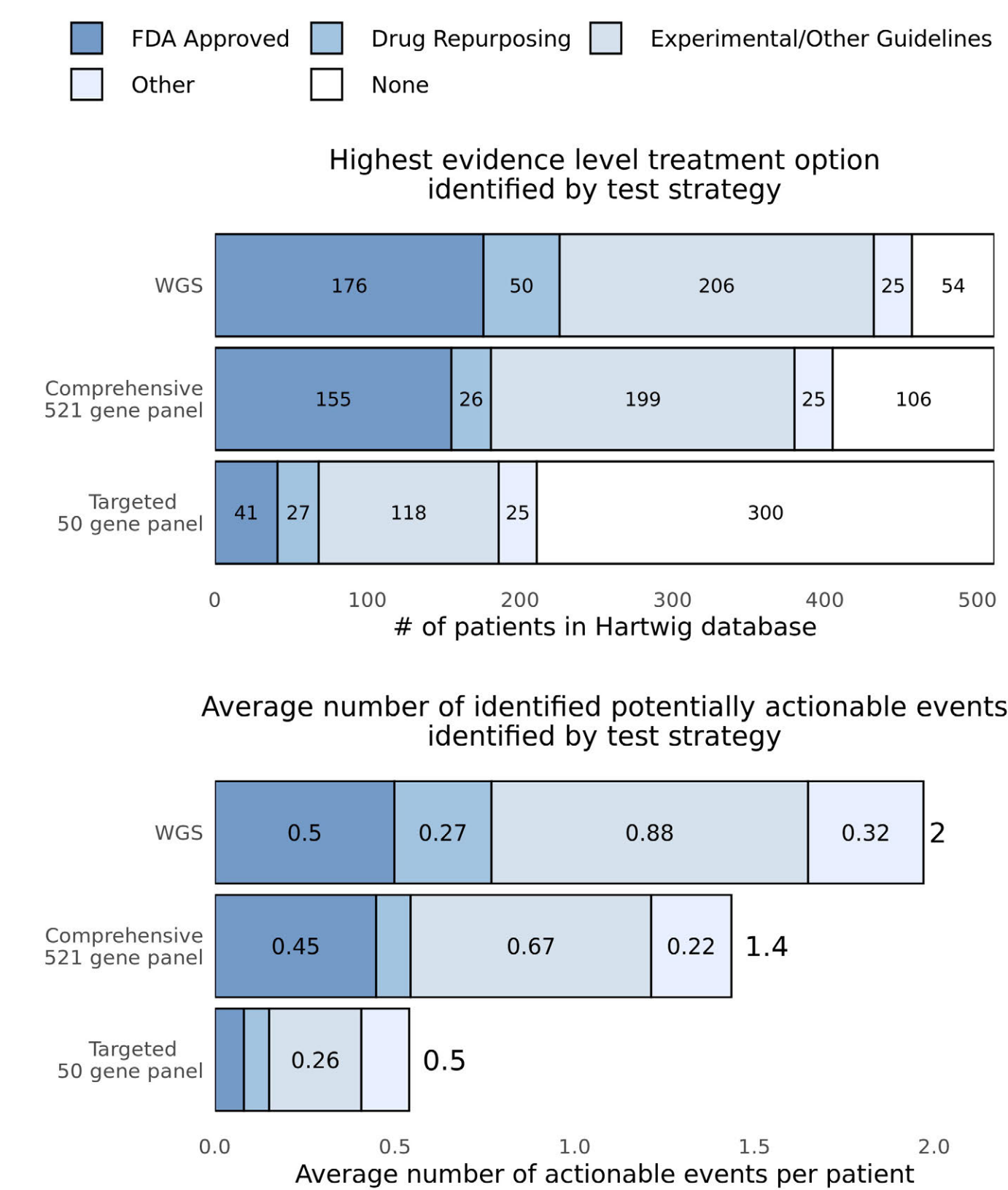### # Events
Somatic drivers: None 9% / None 9%, 6+ 45% / 6+ 44%, 1-5 45% / 1-5 45%
Oncogenes: None 18% / None 18%, 3+ 27% / 3+ 32%, 1-2 55% / 1-2 50%
TSGs: None 9% / None 9%, 3+ 64% / 3+ 61%, 1-2 27% / 1-2 33%

### Summary

| Gene | Type | Penis (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TERT | ONC | 45 | 13 | ▲ |
| TP53 | TSG | 36 | 55 | ▼ |
| FHIT | TSG | 27 | 4.3 | ▲ |
| CD274 | ONC | 18 | 0.6 | ▲ |
| CDKN2A | TSG | 18 | 25 | ▼ |
| FAT1 | TSG | 18 | 1.5 | ▲ |
| JAK2 | ONC | 18 | 1 | ▲ |
| NOTCH1 | TSG | 18 | 1.3 | ▲ |
| PIK3CA | ONC | 18 | 3 | ▲ |
| PTPRD | TSG | 18 | 3 | ▲ |
| ARID1A | TSG | 9.1 | 6 | ▲ |
| CASP8 | TSG | 9.1 | 0.6 | ▲ |
| CCND1 | ONC | 9.1 | 5.6 | ▲ |
| CD44 | ONC | 9.1 | 1 | ▲ |
| CDK4 | ONC | 9.1 | 2 | ▲ |
| CLTC_VMP1 | ONC | 9.1 | 0.3 | ▲ |
| CTNNB1 | ONC | 9.1 | 2.9 | ▲ |
| EGFR | ONC | 9.1 | 5.4 | ▲ |
| ERBB4 | TSG | 9.1 | 0.5 | ▲ |
| FBXW7 | TSG | 9.1 | 2.8 | ▲ |
| FGF3 | ONC | 9.1 | 5.2 | ▲ |
| FOSL2 | ONC | 9.1 | 0.2 | ▲ |
| GSK3B | ONC | 9.1 | 0.1 | ▲ |
| HLA-A | TSG | 9.1 | 0.7 | ▲ |
| IMMP2L | TSG | 9.1 | 0.3 | ▲ |
| KMT2C | TSG | 9.1 | 3.7 | ▲ |
| KRAS | ONC | 9.1 | 15 | ▼ |
| LRRN3 | TSG | 9.1 | 0.2 | ▲ |
| MECOM | ONC | 9.1 | 0.8 | ▲ |

### Top cancer drivers
10 Patients

AMPLIFICATION / DELETION / MUTATION / FUSION

## Potentially Actionable Events

### # Events
Actionable: None 27% / None 18%, 3+ 9% / 3+ 26%, 1-2 64% / 1-2 56%
Best treatment option: None 27% / None 18%, Oth 27% / Oth 14%, Exp 5%, Off 36% / Off 28%, FDA 9% / FDA 36%

### Summary

| Gene | Penis (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CD274 | 18 | 0.5 | ▲ |
| CDKN2A | 18 | 24 | ▼ |
| PIK3CA | 18 | 13 | ▲ |
| CCND1 | 9.1 | 5.3 | ▲ |
| CDK4 | 9.1 | 1.9 | ▲ |
| CTNNB1 | 9.1 | 2.7 | ▲ |
| EGFR | 9.1 | 5.1 | ▲ |
| ERBB4 | 9.1 | 0.5 | ▲ |
| KRAS | 9.1 | 14 | ▼ |
| NOTCH1 | 9.1 | 0.2 | ▲ |
| PTEN | 9.1 | 13 | ▲ |
| TMB High | 9.1 | 21 | ▼ |

### Top potential actionable events
8 Patients

FDA Approved / Drug Repurposing / Other

## Germline Predisposition

### # Events
Germline drivers: None 82% / None 84%, 1+ 18% / 1+ 16%

### Summary

| Gene | Type | Penis (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRIP1 | TSG | 9.1 | 0.2 | ▲ |
| MITF | ONC | 9.1 | 0.7 | ▲ |

### Top potential germline drivers
2 Patients

SMALL_VARIANT

## WGS vs Panel Coverage

FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other / None

### Highest evidence level treatment option identified by test strategy

# of patients in Hartwig database:
- WGS: 1, 2, 2, 4, 2
- Comprehensive 521 gene panel: 1, 2, 2, 2, 4
- Targeted 50 gene panel: 3, 2, 6

### Average number of identified potentially actionable events identified by test strategy

Average number of actionable events per patient:
- WGS: 0.27, 0.82 = 1.4
- Comprehensive 521 gene panel: 0.27, 0.64 = 1.2
- Targeted 50 gene panel: 0.27, 0.45 = 0.7

### Top missed events by Comprehensive Panel vs WGS

FDA Approved / Drug Repurposing

Experimental/Other Guidelines / Other — Partial CN Loss: 2

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved — TMB High: 1
Drug Repurposing

Experimental/Other Guidelines — Full CN Gain: 2
Other — Small Variant: 2, Partial CN Loss: 2

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Prostate Cancer

## Cohort Metadata

### Data availability
Number of patients with data

- WGS: 511
- RNASeq: 326
- Age, Sex: 400
- Biopsy site: 390
- Pretreatment: 368
- Treatment: 326
- Response: 214

### Patients with treatment and response data

| Post-biopsy treatment | | Responders | |
|---|---|---|---|
| Chemo | 88 | 21 (24%) | |
| Multiple | 12 | 4 (33%) | |
| Targeted | 7 | 1 (14%) | |
| Hormonal | 107 | 22 (21%) | |
| Immuno | 14 | 1 (7%) | |
| Radio | 41 | 5 (12%) | |
| Other | 10 | 3 (30%) | |
| None or NA | 0 | 0 | |

## Tumor Characteristics

Prostate / Pan-Cancer

- TMB High: 6% / 21%
- MSI High: 5% / 2%
- WGD: 56% / 56%
- Diploid Proportion: 33% / 34%
- GIE HLA LOH: 5% / 19%
- GIE Overall: 15% / 26%
- Viral Insertions: 0% / 3%
- HRD: 11% / 6%

## Mutational Landscape

### Tumor purity
63% / 55%

### Clonal mutation fraction
94% / 95%

### Tumor mutational burden
2.8 / 4.2
High 6% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 6,702 | 992 / 983 | 288 / 183 | 92 / 50 |

Number of variants vs Quantile

### Telomere Length
0.8 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
5 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.19 / 0.15
Instable 5% / 2%
MS indels per megabase

### Mean genome ploidy
3 / 2.6

### Aneuploidy Score
21 / 16

### % Copy number alteration
68% / 54%

### % Genome LOH
20% / 24%

## Processes Underlying Mutations

- DNA damage repair: 38%
- Ageing: 16%
- Chemical exposure: 7%
- Tobacco: 3%
- APOBEC: 2%
- UV light: 1%
- Unknown: 32%

Prostate 511 Patients
Pan-Cancer 6790 Patients

Prostate

## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events

| | Prostate | Pan-Cancer |
|---|---|---|
| Somatic drivers | 6+ 50% / 44% | |
| | 1-5 50% / 54% | |
| Oncogenes | None 6% / 18% | |
| | 3+ 38% / 32% | |
| | 1-2 55% / 50% | |
| TSGs | 3+ 66% / 61% | |
| | 1-2 33% / 33% | |

### Summary

| Gene | Type | Prostate (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|---|
| TP53 | TSG | 56 | 55 | |
| AR | ONC | 55 | 5.6 | ▲ |
| PTEN | TSG | 49 | 14 | ▲ |
| TMPRSS2_ERG | ONC | 45 | 3.5 | ▲ |
| RB1 | TSG | 14 | 11 | |
| KDM6A | TSG | 10 | 3.7 | ▲ |
| APC | TSG | 8.4 | 14 | ▼ |
| CHD1 | TSG | 7.8 | 0.6 | ▲ |
| ATM | TSG | 7.6 | 2.9 | |
| FOXA1 | ONC | 7.6 | 2.3 | ▲ |
| KMT2C | TSG | 7.4 | 3.7 | |
| ZMYM3 | TSG | 6.7 | 0.8 | ▲ |
| CTNNB1 | ONC | 6.5 | 2.9 | |
| SPOP | ONC | 6.5 | 1.3 | ▲ |
| BRCA2 | TSG | 6.3 | 1.2 | ▲ |
| JAK1 | TSG | 6.3 | 1.1 | ▲ |
| CDK12 | TSG | 5.5 | 0.9 | ▲ |
| MYC | ONC | 5.5 | 5.7 | |
| ZFP36L2 | TSG | 5.5 | 2.4 | |
| PIK3CA | ONC | 5.3 | 13 | ▼ |
| TMPRSS2 | ONC | 5.3 | 0.5 | ▲ |
| ZFHX3 | TSG | 5.3 | 1.1 | ▲ |
| NCOA2 | ONC | 4.9 | 1.6 | |
| NCOR1 | TSG | 4.7 | 1.6 | |
| CDKN2A | TSG | 4.3 | 25 | ▼ |
| ZMIZ1 | ONC | 4.3 | 1.3 | ▲ |
| KMT2D | TSG | 4.1 | 2.9 | |
| PREX2 | ONC | 3.9 | 1.6 | |
| PABPC1 | ONC | 3.7 | 2.3 | |

Top cancer drivers — 507 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events

| | Prostate | Pan-Cancer |
|---|---|---|
| Actionable | None 13% / 18% | |
| | 3+ 24% / 26% | |
| | 1-2 63% / 56% | |
| Best treatment option | None 13% / 18% | |
| | Oth 41% / 14% | |
| | Exp 4% / 5% | |
| | Off 8% / 28% | |
| | FDA 35% / 36% | |

### Summary

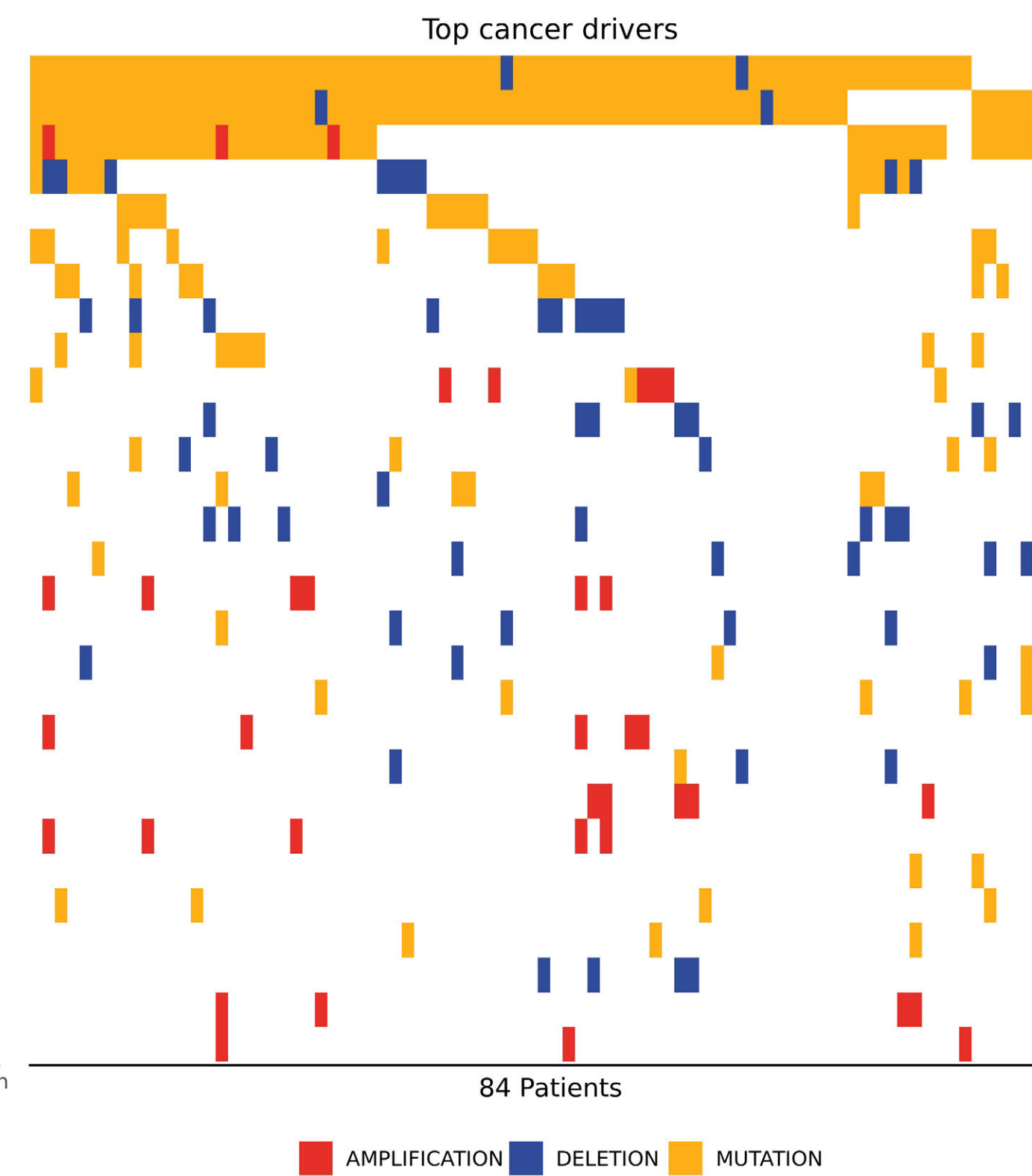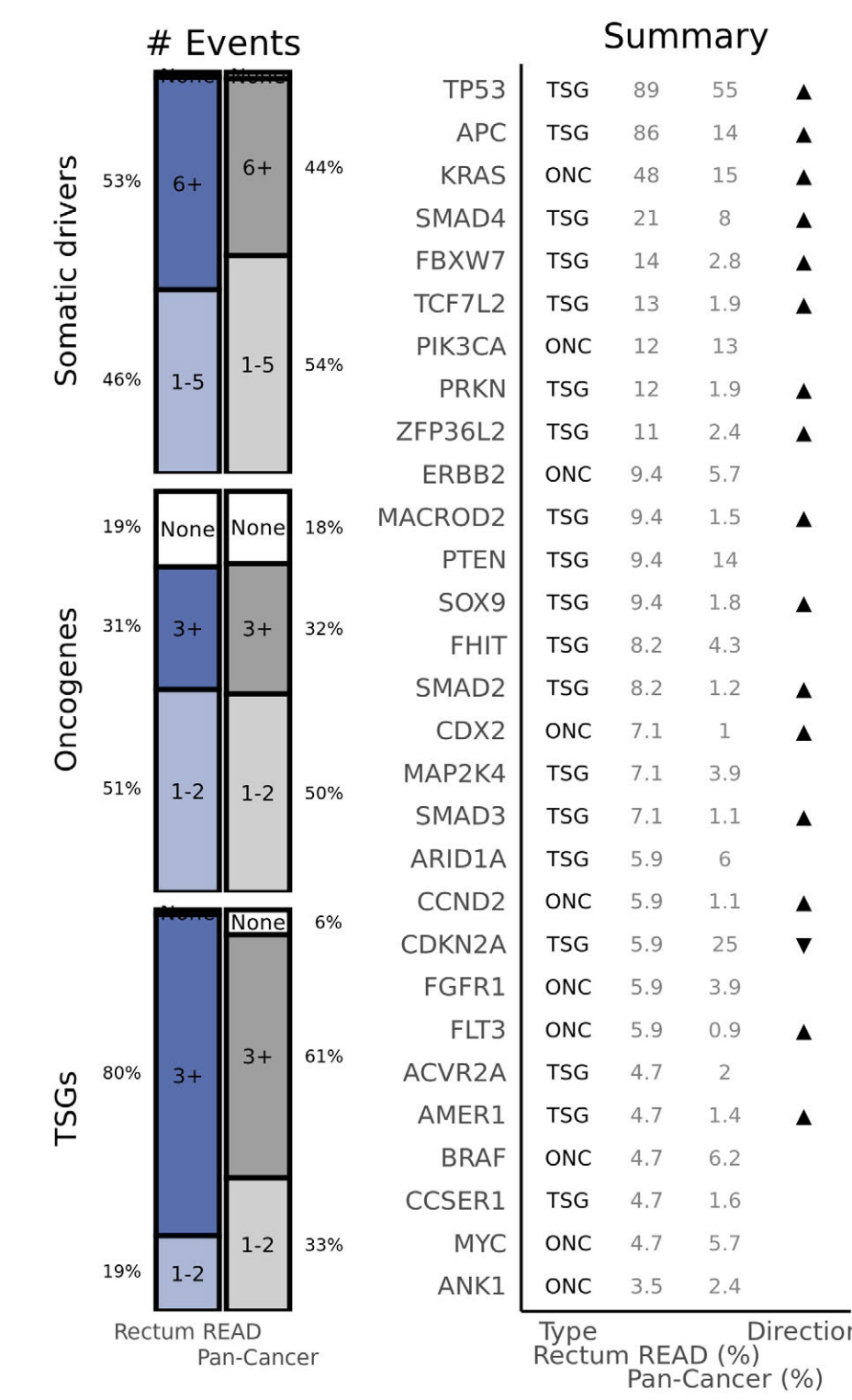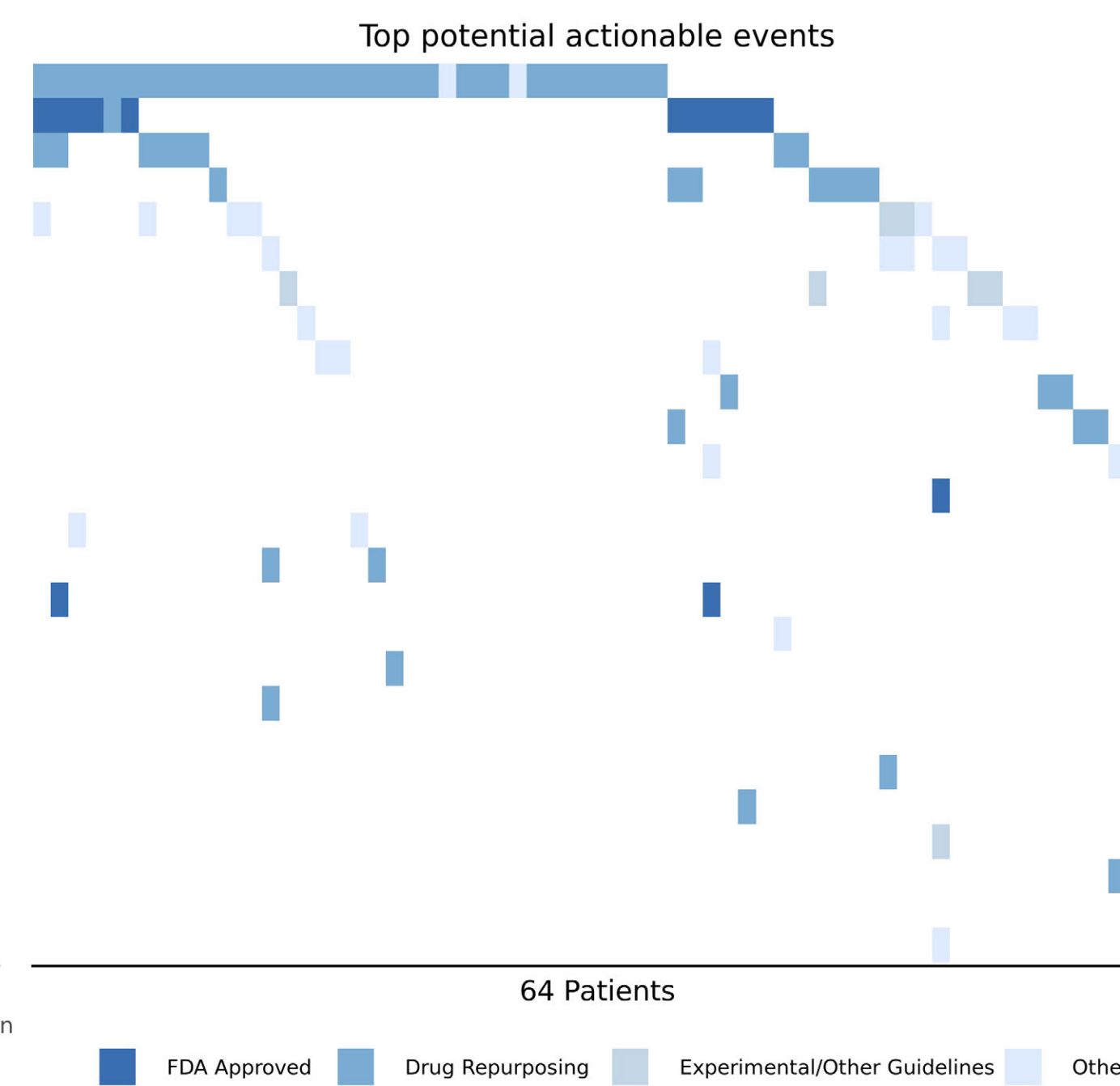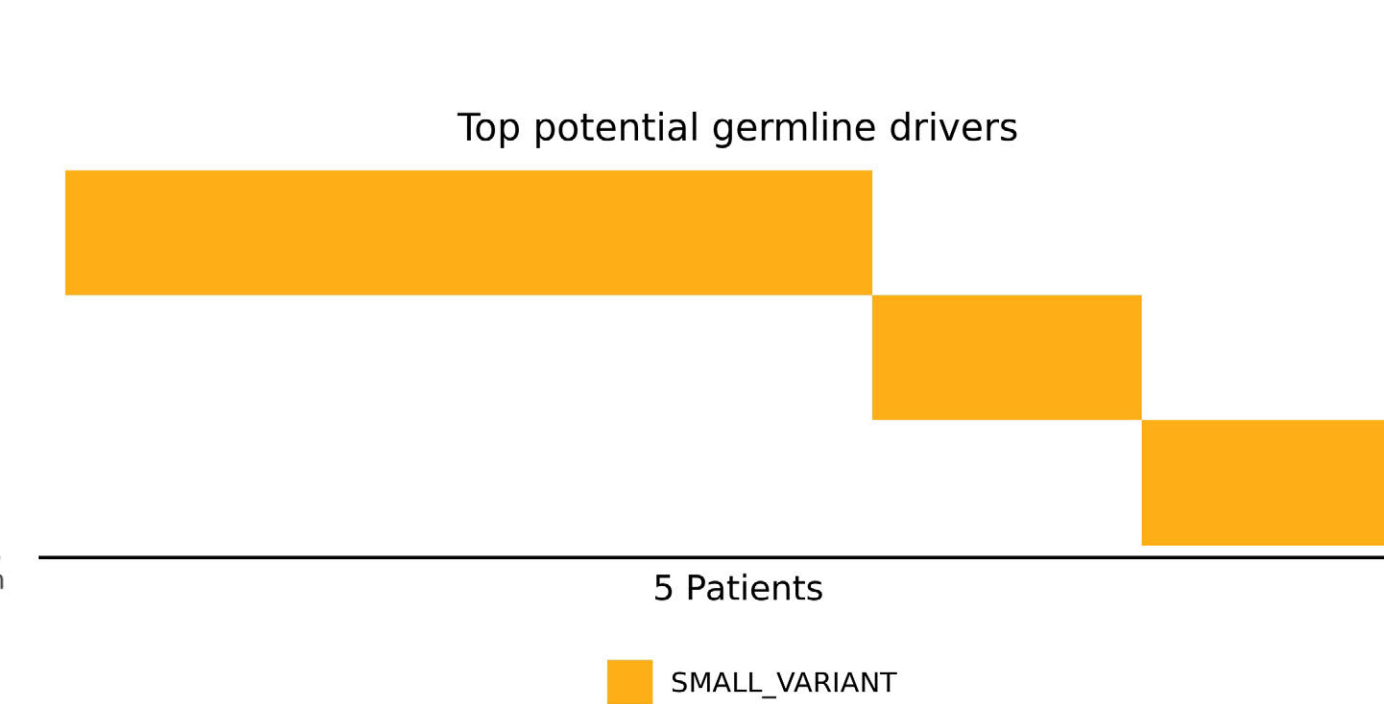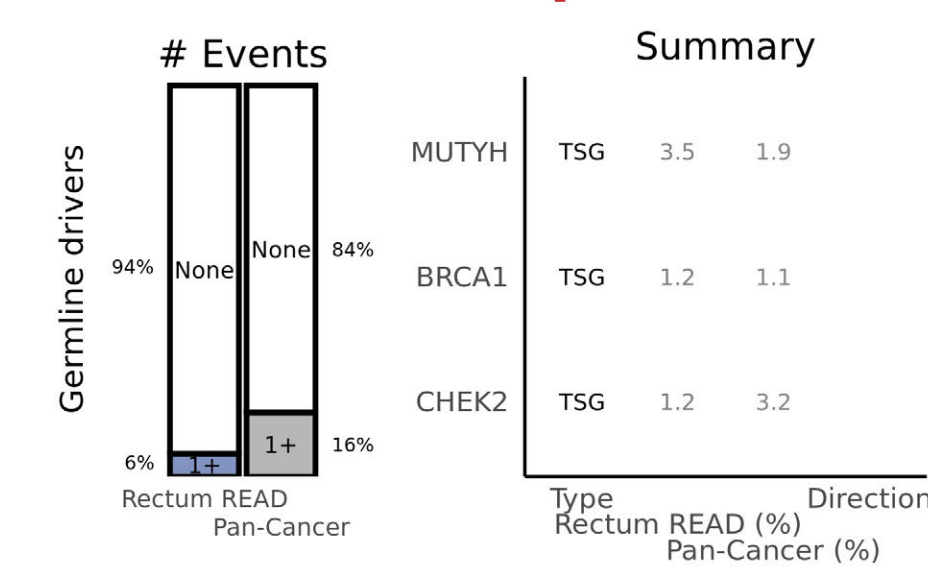| Gene | Prostate (%) | Pan-Cancer (%) | Dir |
|---|---|---|---|
| PTEN | 48 | 13 | ▲ |
| AR | 34 | 2.8 | ▲ |
| HR deficiency | 11 | 5.8 | |
| ATM | 8.8 | 3.5 | ▲ |
| BRCA2 | 8.6 | 2.4 | ▲ |
| TMB High | 7 | 21 | ▼ |
| CTNNB1 | 6.1 | 2.7 | |
| MSI High | 6.1 | 3.1 | |
| CDK12 | 4.9 | 0.9 | ▲ |
| PIK3CA | 4.9 | 13 | ▼ |
| CDKN2A | 4.3 | 24 | ▼ |
| CHEK2 | 4.1 | 3 | |
| KMT2D | 4.1 | 2.9 | |
| FGFR1 | 2.7 | 3.8 | |
| CCND1 | 2.3 | 5.3 | |
| BRAF | 2.2 | 5.9 | |
| AKT1 | 2 | 1.4 | |
| RAD51B | 1.6 | 0.7 | |
| HRAS | 1.2 | 0.6 | |
| BRCA1 | 1 | 1.3 | |
| KRAS | 1 | 14 | ▼ |
| FGFR3 | 0.8 | 1.2 | |
| RAD51C | 0.8 | 0.1 | ▲ |
| Rest FDA | 2.2 | | |
| Rest Repurpose | 4.9 | | |
| Rest Experimental | 1.4 | | |
| Rest Other | 2 | | |

Top potential actionable events — 447 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events

| | Prostate | Pan-Cancer |
|---|---|---|
| Germline drivers | None 81% / 84% | |
| | 1+ 19% / 16% | |

### Summary

| Gene | Type | Prostate (%) | Pan-Cancer (%) |
|---|---|---|---|
| CHEK2 | TSG | 3.9 | 3.2 |
| BRCA2 | TSG | 3.1 | 1.5 |
| MUTYH | TSG | 2.3 | 1.9 |
| ATM | TSG | 1.8 | 1 |
| MSH2 | TSG | 1 | 1 |
| MITF | ONC | 0.8 | 0.7 |
| RAD50 | TSG | 0.8 | 0.5 |
| TP53 | TSG | 0.8 | 0.5 |
| NTHL1 | TSG | 0.6 | 0.4 |

Top potential germline drivers — 73 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy

| Strategy | | | | | |
|---|---|---|---|---|---|
| WGS | 176 | 50 | 206 | 25 | 54 |
| Comprehensive 521 gene panel | 155 | 26 | 199 | 25 | 106 |
| Targeted 50 gene panel | 41 | 27 | 118 | 25 | 300 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.5 | 0.27 | 0.88 | 0.32 | 2 |
| Comprehensive 521 gene panel | 0.45 | | 0.67 | 0.22 | 1.4 |
| Targeted 50 gene panel | 0.26 | | 0.5 | | |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
- Partial CN Loss: 17
- HMZ Disruption: 5
- Fusion: 4

Drug Repurposing:
- HRD: 55
- Partial CN Loss: 17
- Fusion: 16
- HMZ Disruption: 1

Experimental/Other Guidelines:
- Partial CN Loss: 87
- Partial CN Gain: 10
- Small Variant: 4
- Fusion: 3
- Full CN Loss: 2

Other:
- HMZ Disruption: 34
- Partial CN Loss: 7
- Full CN Loss: 5
- Small Variant: 4

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved:
- Small Variant: 118
- TMB High: 36
- Partial CN Loss: 17
- Full CN Loss: 17
- Splice Site: 17

Drug Repurposing:
- HRD: 55
- Partial CN Loss: 17
- Fusion: 16
- Small Variant: 13
- HMZ Disruption: 1

Experimental/Other Guidelines:
- Full CN Gain: 174
- Partial CN Loss: 87
- Full CN Loss: 21
- Partial CN Gain: 17
- Small Variant: 15

Other:
- Small Variant: 46
- HMZ Disruption: 34
- Partial CN Loss: 7
- Full CN Loss: 6
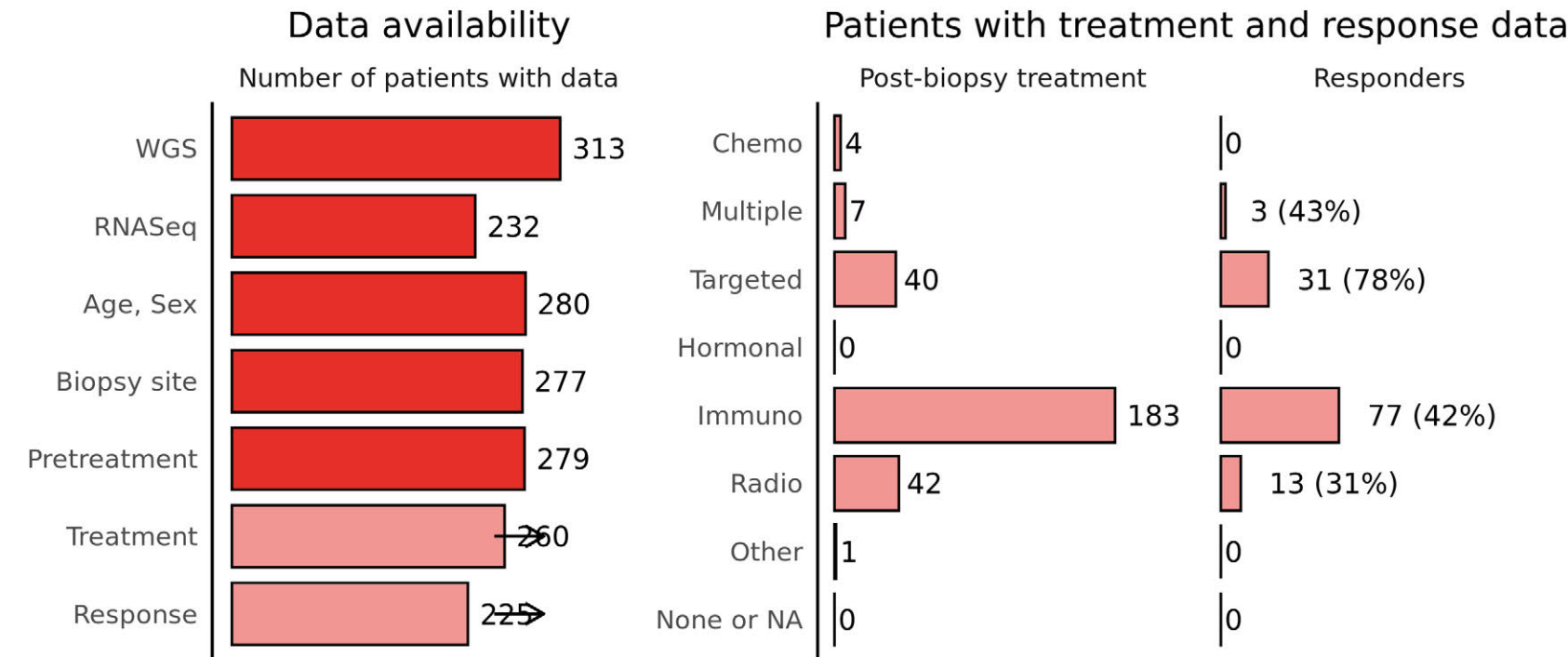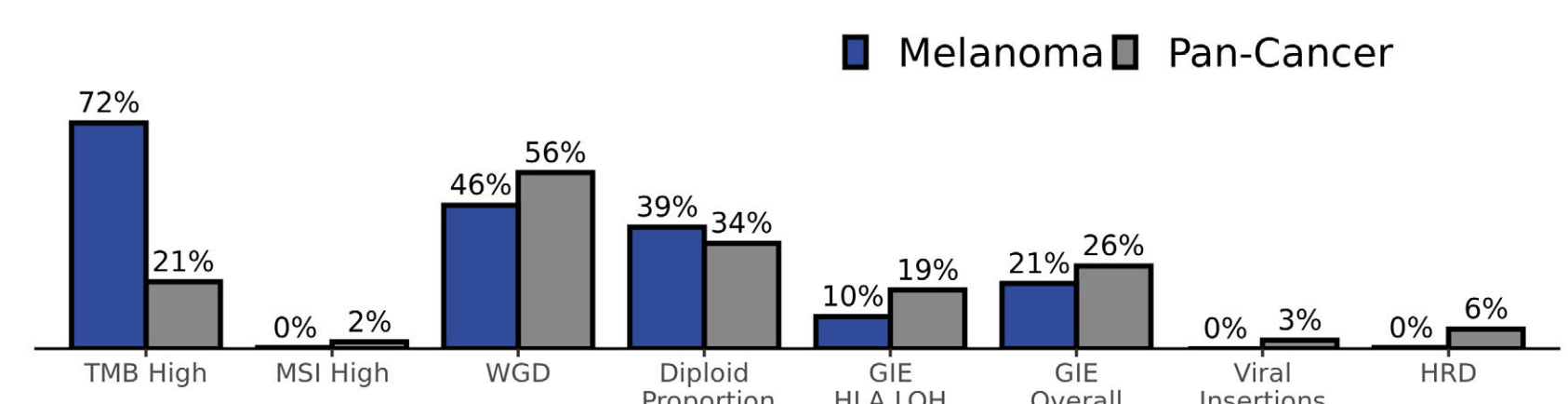- Splice Site: 3

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Rectal Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

- WGS — 85
- RNASeq — 20
- Age, Sex — 19
- Biopsy site — 18
- Pretreatment — 9
- Treatment — 9
- Response — 8

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

- Chemo — 4 / 0
- Multiple — 1 / 0
- Targeted — 3 / 1 (33%)
- Hormonal — 0 / 0
- Immuno — 0 / 0
- Radio — 1 / 0
- Other — 0 / 0
- None or NA — 0 / 0

## Tumor Characteristics

Legend: Rectum READ (blue), Pan-Cancer (grey)

- TMB High: 20% / 21%
- MSI High: 2% / 2%
- WGD: 67% / 56%
- Diploid Proportion: 26% / 34%
- GIE HLA LOH: 21% / 19%
- GIE Overall: 25% / 26%
- Viral Insertions: 0% / 3%
- HRD: 2% / 6%

## Mutational Landscape

### Tumor purity
56% / 55%

### Clonal mutation fraction
96% / 95%

### Tumor mutational burden
7.1 / 4.2 — TMB per Megabase; High 20% / 21%

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Rectum READ | 18,197 | 2,089 | 218 | 200 |
| Pan-Cancer | 10,846 | 983 | 183 | 92 |

Number of variants vs Quantile

### Telomere Length
0.86 / 0.82 — Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
7 / 6 — Log2 (CDR3 + 1)

### Microsatellite instability
0.49 / 0.15 — MS indels per megabase; Instable 2% / 2%

### Mean genome ploidy
2.8 / 2.6

### Aneuploidy Score
20 / 16

### % Copy number alteration
61% / 54%

### % Genome LOH
28% / 24%

## Processes Underlying Mutations

- DNA damage repair: 22%
- Chemical exposure: 14%
- Ageing: 13%
- APOBEC: 3%
- Tobacco: 2%
- UV light: 1%
- Unknown: 45%

Rectum READ 85 Patients — Pan-Cancer 6790 Patients — Colorectal

## Copy Number Alteration Profile

(circos plot; labeled genes include PHF20B, GNAS, MACROD2, SMAD4, SMAD2, TOP2A, SOX9, ERBB2, MAP2K4, TP53, SMAD3, IRS2, FLT3, CDX2, ARID1A, KRAS, CCND2, PTEN, ZMIZ1, MYC, CDKN2A, FGF2, CCND1, FGFR1, AFF3, MET, PRKN, APC, RASA1, LINC00290, PTPN13, CCSER1, CTNNB1, FHIT)

## Cancer Driver Landscape

### # Events / Summary

| | | Type | Rectum READ (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|---|
| Somatic drivers | 6+: 53%/44%; 1-5: 46%/54% | | | | |
| TP53 | | TSG | 89 | 55 | ▲ |
| APC | | TSG | 86 | 14 | ▲ |
| KRAS | | ONC | 48 | 15 | ▲ |
| SMAD4 | | TSG | 21 | 8 | ▲ |
| FBXW7 | | TSG | 14 | 2.8 | ▲ |
| TCF7L2 | | TSG | 13 | 1.9 | ▲ |
| PIK3CA | | ONC | 12 | 13 | |
| PRKN | | TSG | 12 | 1.9 | ▲ |
| ZFP36L2 | | TSG | 11 | 2.4 | ▲ |
| ERBB2 | | ONC | 9.4 | 5.7 | |
| MACROD2 | | TSG | 9.4 | 14 | |
| PTEN | | TSG | 9.4 | 14 | |
| SOX9 | | TSG | 9.4 | 3.9 | ▲ |
| FHIT | | TSG | 8.2 | 4.3 | |
| SMAD2 | | TSG | 8.2 | 1.2 | ▲ |
| CDX2 | | ONC | 7.1 | 1 | ▲ |
| MAP2K4 | | TSG | 7.1 | 3.9 | |
| SMAD3 | | TSG | 7.1 | 1.1 | ▲ |
| ARID1A | | TSG | 5.9 | 6 | |
| CCND2 | | ONC | 5.9 | 1.1 | ▲ |
| CDKN2A | | ONC | 5.9 | 25 | ▼ |
| FGFR1 | | ONC | 5.9 | 3.9 | |
| FLT3 | | ONC | 5.9 | 0.9 | |
| ACVR2A | | TSG | 4.7 | 2 | ▲ |
| AMER1 | | TSG | 4.7 | 1.4 | ▲ |
| BRAF | | ONC | 4.7 | 6.2 | |
| CCSER1 | | TSG | 4.7 | 1.6 | |
| MYC | | ONC | 4.7 | 5.7 | |
| ANK1 | | ONC | 3.5 | 2.4 | |

Oncogenes: None 19%/18%; 3+ 31%/32%; 1-2 51%/50%
TSGs: 3+ 80%/61%; 1-2 19%/33%

Top cancer drivers — 84 Patients

Legend: AMPLIFICATION (red), DELETION (blue), MUTATION (orange)

## Potentially Actionable Events

### # Events / Summary

| | Rectum READ (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| KRAS | 42 | 14 | ▲ |
| TMB High | 14 | 21 | ▼ |
| PIK3CA | 9.4 | 13 | |
| ERBB2 | 8.2 | 5.6 | |
| PTEN | 8.2 | 13 | ▼ |
| CDKN2A | 5.9 | 24 | ▼ |
| BRAF | 4.7 | 5.9 | |
| FGFR1 | 4.7 | 3.8 | |
| CTNNB1 | 3.5 | 2.7 | |
| MET | 3.5 | 1.7 | |
| NRAS | 3.5 | 2.6 | |
| CCND1 | 2.4 | 5.3 | |
| EGFR | 2.4 | 5.1 | |
| ERBB4 | 2.4 | 0.5 | ▲ |
| HR deficiency | 2.4 | 5.8 | |
| MSI High | 2.4 | 3.1 | |
| AR | 1.2 | 2.8 | |
| ATM | 1.2 | 3.5 | ▼ |
| BRCA1 | 1.2 | 1.3 | |
| CHEK2 | 1.2 | 3 | |
| KIT | 1.2 | 1.1 | |
| MAP2K1 | 1.2 | 0.8 | |
| NF1 | 1.2 | 0.4 | |
| Rest Repurpose | | 1.2 | |
| Rest Experimental | | 1.2 | |
| Rest Other | | 1.2 | |

Actionable: None 25%/18%; 3+ 11%/26%; 1-2 65%/56%
Best treatment option: None 25%/18%; Oth 7%/14%; Exp 4%/5%; Off 49%/28%; FDA 15%/36%

Top potential actionable events — 64 Patients

Legend: FDA Approved (dark blue), Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events / Summary

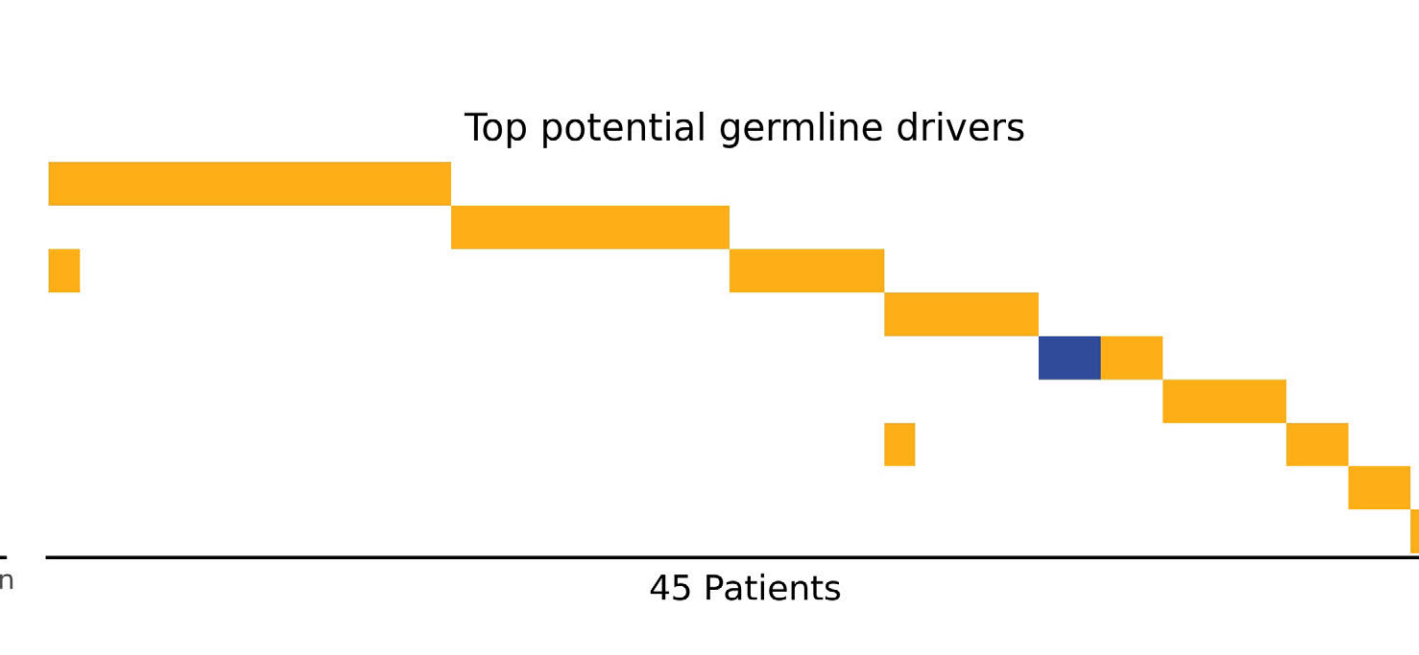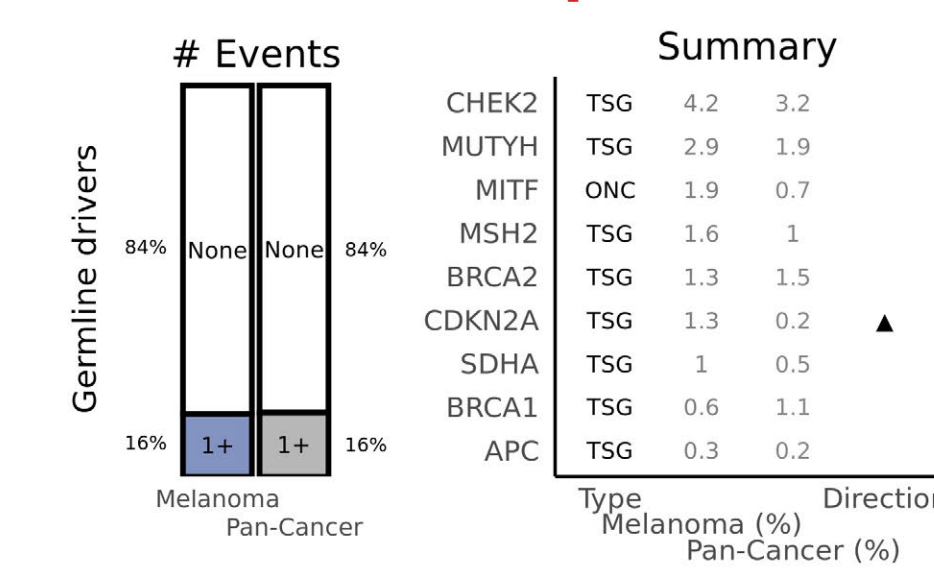| | Type | Rectum READ (%) | Pan-Cancer (%) |
|---|---|---|---|
| MUTYH | TSG | 3.5 | 1.9 |
| BRCA1 | TSG | 1.2 | 1.1 |
| CHEK2 | TSG | 1.2 | 3.2 |

Germline drivers: None 94%/84%; 1+ 6%/16%

Top potential germline drivers — 5 Patients

Legend: SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

(# of patients in Hartwig database)

- WGS: 13 | 43 | 8 | 20
- Comprehensive 521 gene panel: 13 | 40 | 7 | 23
- Targeted 50 gene panel: 47 | 6 | 28

### Average number of identified potentially actionable events identified by test strategy

(Average number of actionable events per patient)

- WGS: 0.79 | 0.36 — 1.5
- Comprehensive 521 gene panel: 0.73 | 0.26 — 1.3
- Targeted 50 gene panel: 0.67 — 0.9

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved** — Partial CN Loss
**Drug Repurposing** — Partial CN Loss 2; HRD 2; Fusion 1
**Experimental/Other Guidelines** — Partial CN Loss 8; Fusion 1
**Other** — Partial CN Loss 2; HMZ Disruption 1

### Top missed events by Targeted Panel vs WGS

**FDA Approved** — TMB High 11; Small Variant 2
**Drug Repurposing** — Small Variant 4; Partial CN Loss 2; HRD 2; Fusion 1; TMB High 1
**Experimental/Other Guidelines** — Full CN Gain 9; Partial CN Loss 8; Small Variant 3; Full CN Loss 2; Fusion 1
**Other** — Small Variant 4; Partial CN Loss 2; HMZ Disruption 1

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Skin Basal Cell Carcinoma

## Cohort Metadata

### Data availability
**Number of patients with data**

| | |
|---|---|
| WGS | 17 |
| RNASeq | 7 |
| Age, Sex | 8 |
| Biopsy site | 6 |
| Pretreatment | 5 |
| Treatment | 4 |
| Response | 3 |

### Patients with treatment and response data
**Post-biopsy treatment** / **Responders**

| | Treatment | Responders |
|---|---|---|
| Chemo | 0 | 0 |
| Multiple | 0 | 0 |
| Targeted | 3 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 1 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: ■ Skin SKBCC ■ Pan-Cancer

| | Skin SKBCC | Pan-Cancer |
|---|---|---|
| TMB High | 88% | 21% |
| MSI High | 0% | 2% |
| WGD | 31% | 56% |
| Diploid Proportion | 58% | 34% |
| GIE HLA LOH | 25% | 19% |
| GIE Overall | 44% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
65% / 55%

### Clonal mutation fraction
98% / 95%

### Tumor mutational burden
30 — 88% High
4 — 21%
TMB per Megabase

### Variant types
Number of variants / Quantile

- SNV: 82,396 / 10,846
- INDEL: 1,150 / 983
- Structural: 191 / 183
- MNV: 2,171 / 92

### Telomere Length
1.4 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
4 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.19 — 0%
0.15 — Instable 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
5 / 16

### % Copy number alteration
19% / 54%

### % Genome LOH
11% / 24%

## Processes Underlying Mutations

- UV light: 88%
- APOBEC: 2%
- Chemical exposure: 1%
- DNA damage repair: 1%
- Ageing: 0%
- Tobacco: 0%
- Unknown: 7%

Skin SKBCC — 17 Patients
Pan-Cancer — 6790 Patients

Skin

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## Copy Number Alteration Profile

(circos plot: RUNX1, IL6ST, PIK3R1, CDK4, ERBB3, PTCH1, CDKN2A, JAK2, CYLD)

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers**

| Gene | Type | Skin SKBCC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| PTCH1 | TSG | 88 | 0.5 | ▲ |
| TERT | ONC | 71 | 13 | ▲ |
| TP53 | TSG | 53 | 55 | ▲ |
| ARID1A | TSG | 29 | 6 | ▲ |
| SMO | ONC | 18 | 0.2 | ▲ |
| CASZ1 | TSG | 12 | 0.6 | ▲ |
| CTNNB1 | ONC | 12 | 2.9 | ▲ |
| GRIN2A | TSG | 12 | 0.5 | ▲ |
| KMT2B | TSG | 12 | 1 | ▲ |
| NOTCH1 | TSG | 12 | 1.3 | ▲ |
| AMER1 | TSG | 5.9 | 1.4 | ▲ |
| ARHGAP35 | TSG | 5.9 | 0.6 | ▲ |
| AXIN1 | TSG | 5.9 | 0.6 | ▲ |
| BAP1 | TSG | 5.9 | 2.7 | ▲ |
| CDK4 | ONC | 5.9 | 0.3 | ▲ |
| CDKN2A | TSG | 5.9 | 25 | ▼ |
| CUX1 | TSG | 5.9 | 0.3 | ▲ |
| CYLD | TSG | 5.9 | 1.9 | ▲ |
| ERBB3 | ONC | 5.9 | 0.8 | ▲ |
| FAT1 | TSG | 5.9 | 1.5 | ▲ |
| FBXO11 | TSG | 5.9 | 0.3 | ▲ |
| FGFR2 | TSG | 5.9 | 1.2 | ▲ |
| FOSL2 | TSG | 5.9 | 0.2 | ▲ |
| G6PD | TSG | 5.9 | 0.1 | ▲ |
| IL6ST | TSG | 5.9 | 0.5 | ▲ |
| JAK2 | ONC | 5.9 | 1 | ▲ |
| KMT2D | TSG | 5.9 | 2.9 | ▲ |
| MAP2K1 | ONC | 5.9 | 0.9 | ▲ |
| MPDZ_NFIB | TSG | 5.9 | 0 | ▲ |

Somatic drivers: 35% / 44%; 65% / 18%
Oncogenes: 12% / 32%; 6% / 50%; 82%
TSGs: 6%; 76% / 61%; 18% / 33%

Top cancer drivers — 17 Patients

Legend: ■ AMPLIFICATION ■ DELETION ■ MUTATION ■ FUSION

## Potentially Actionable Events

### # Events / Summary

**Actionable**

| Gene | Skin SKBCC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PTCH1 | 76 | 0.5 | ▲ |
| TMB High | 76 | 21 | ▲ |
| CTNNB1 | 12 | 2.7 | ▲ |
| CDK4 | 5.9 | 1.9 | ▲ |
| CDKN2A | 5.9 | 24 | ▼ |
| FGFR2 | 5.9 | 1.1 | ▲ |
| KMT2D | 5.9 | 2.9 | ▲ |
| PTEN | 5.9 | 13 | ▼ |

Actionable: 12% / 18%; 29% / 26%; 59% / 56%
Best treatment option: 12% / 18%; 6%; 6%; 5%; 28%; 76% / 36%

Top potential actionable events — 15 Patients

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events / Summary

| Gene | Type | Skin SKBCC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MSH2 | TSG | 5.9 | 1 | ▲ |

Germline drivers: 94% / 84% None; 6% / 16%

Top potential germline drivers — 1 Patients

Legend: ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved ■ Drug Repurposing ■ Other ■ Experimental/Other Guidelines □ None

### Highest evidence level treatment option identified by test strategy

| Test strategy | Values |
|---|---|
| WGS | 13 / 1 / 1 / 2 |
| Comprehensive 521 gene panel | 13 / 1 / 1 / 2 |
| Targeted 50 gene panel | 1 / 2 / 14 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | Values | Total |
|---|---|---|
| WGS | 0.76 / 1 / 0.41 | 2.2 |
| Comprehensive 521 gene panel | 0.76 / 0.82 / 0.41 | 2.1 |
| Targeted 50 gene panel | 0.2 | |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

- FDA Approved: (none)
- Drug Repurposing: (none)
- Experimental/Other Guidelines: Small Variant 1; HMZ Disruption 1; Partial CN Loss 1
- Other: (none)

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

- FDA Approved: TMB High 13
- Drug Repurposing: (none)
- Experimental/Other Guidelines: Small Variant 10; Splice Site 4; Full CN Gain 1; HMZ Disruption 1; Partial CN Loss 1
- Other: Small Variant 4

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: min ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red); moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
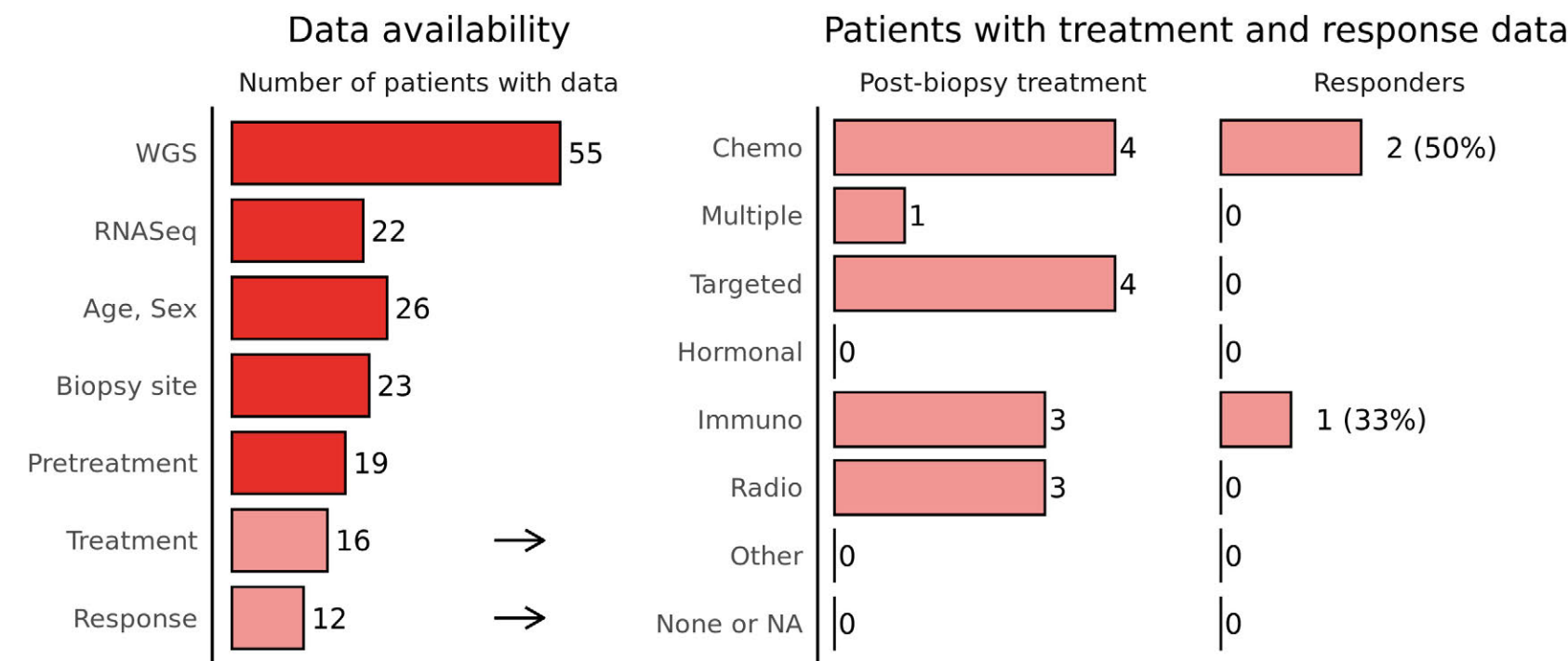Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: SKBCC
DOIDs included: 2513
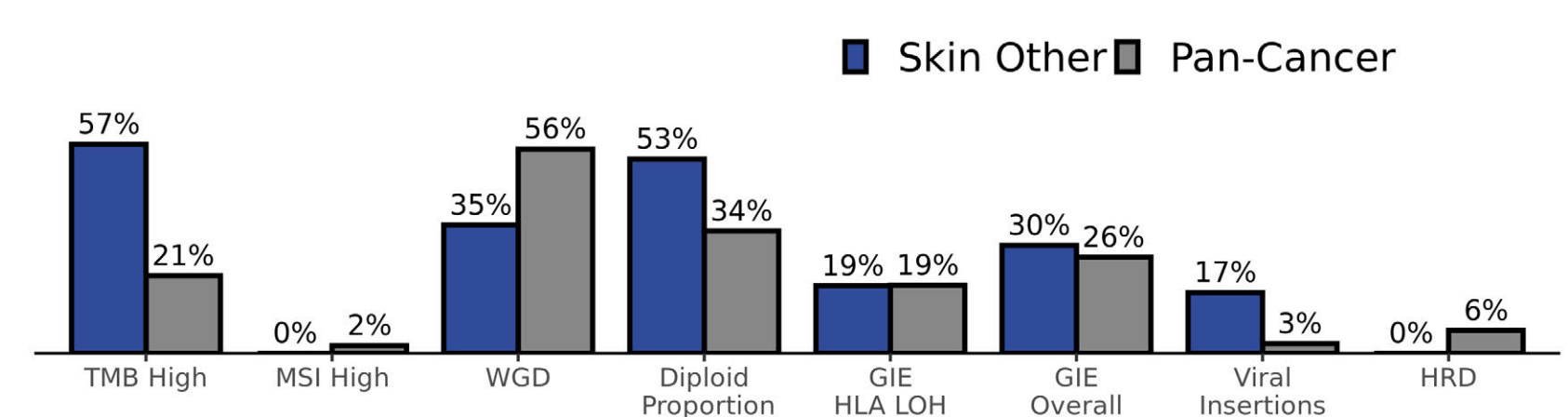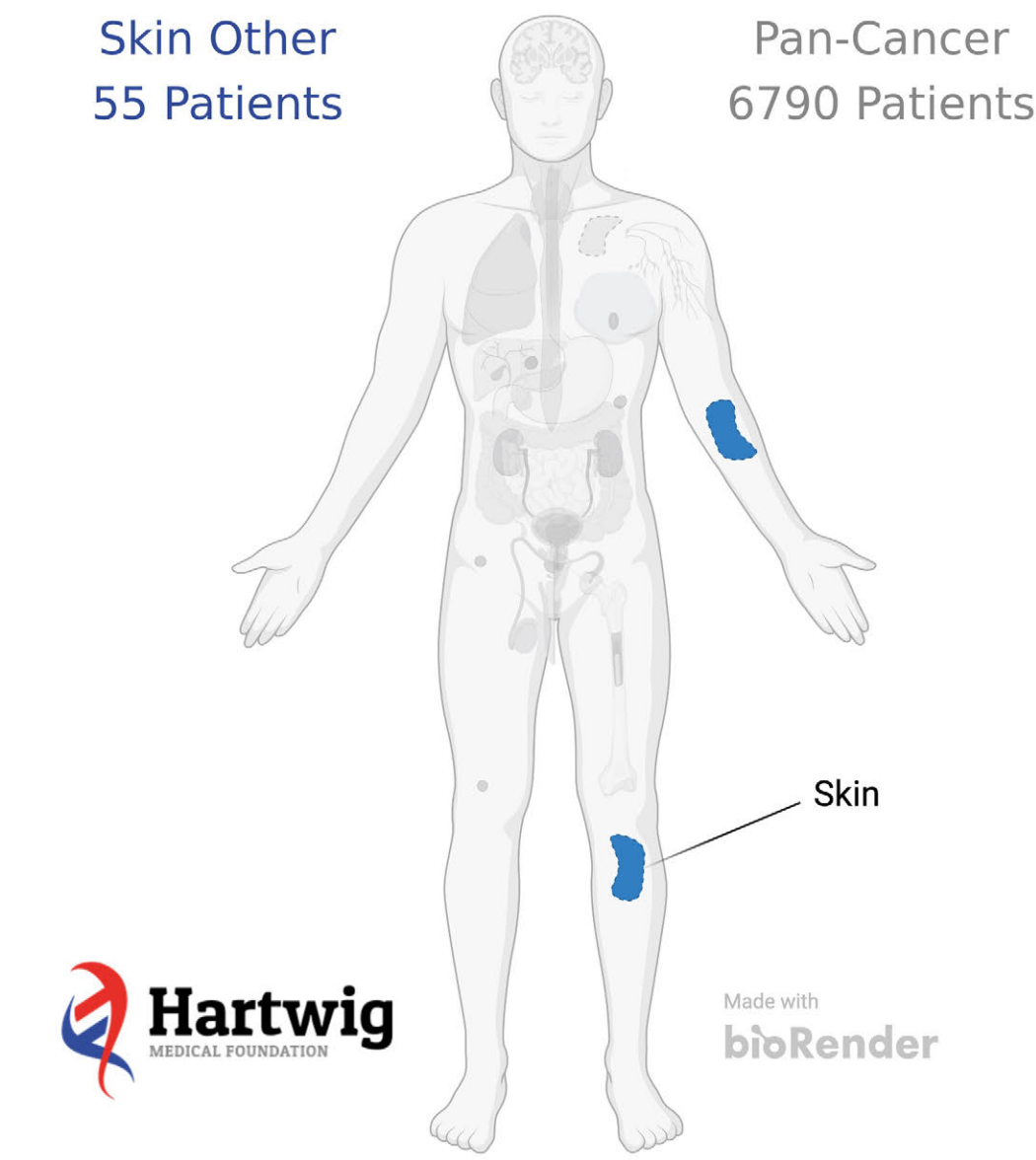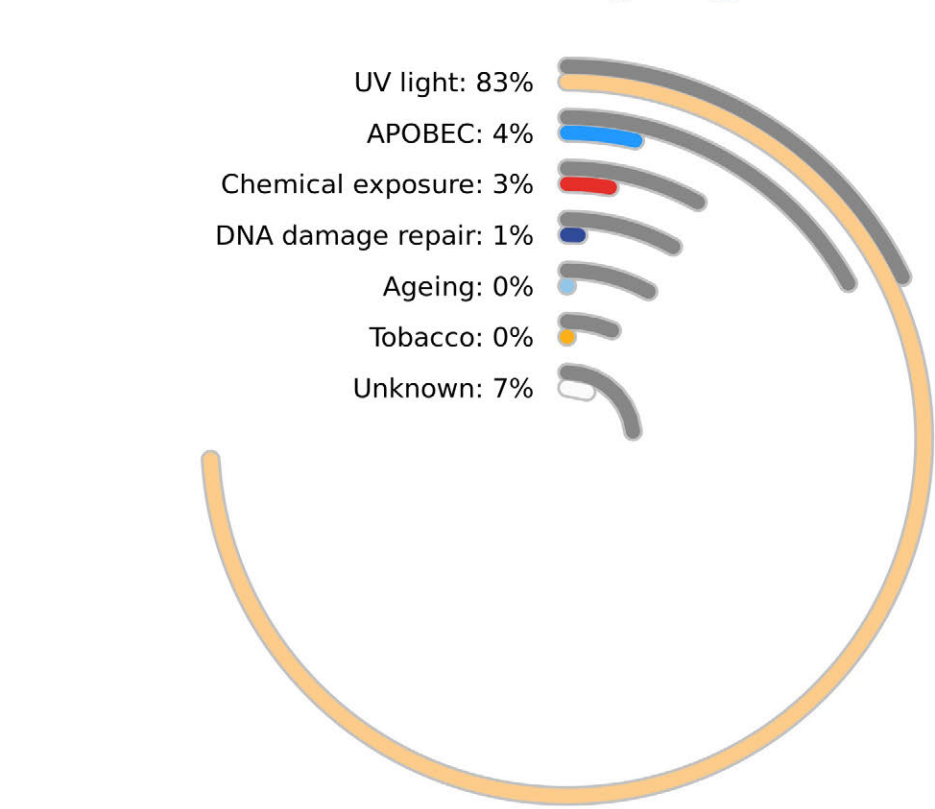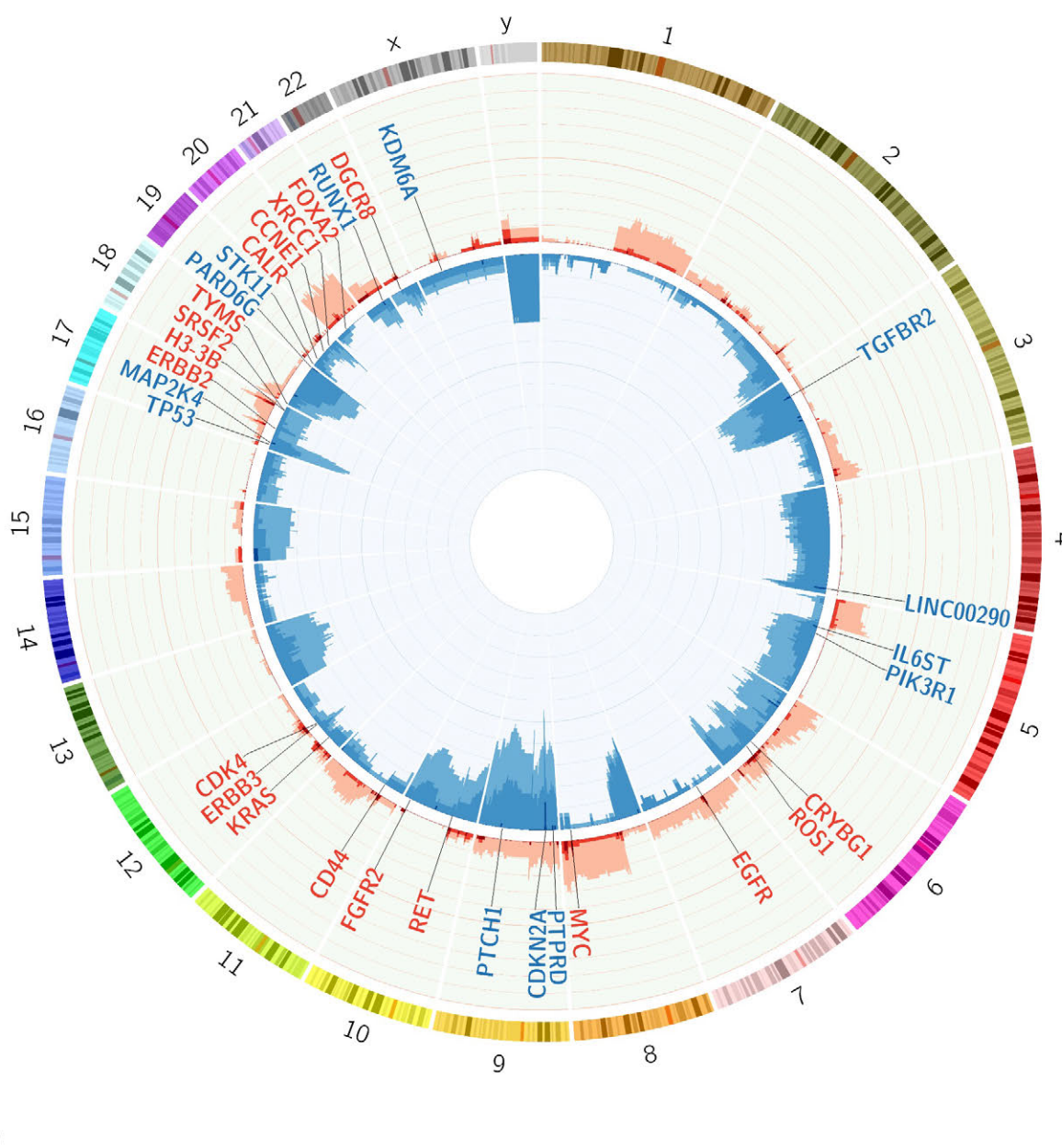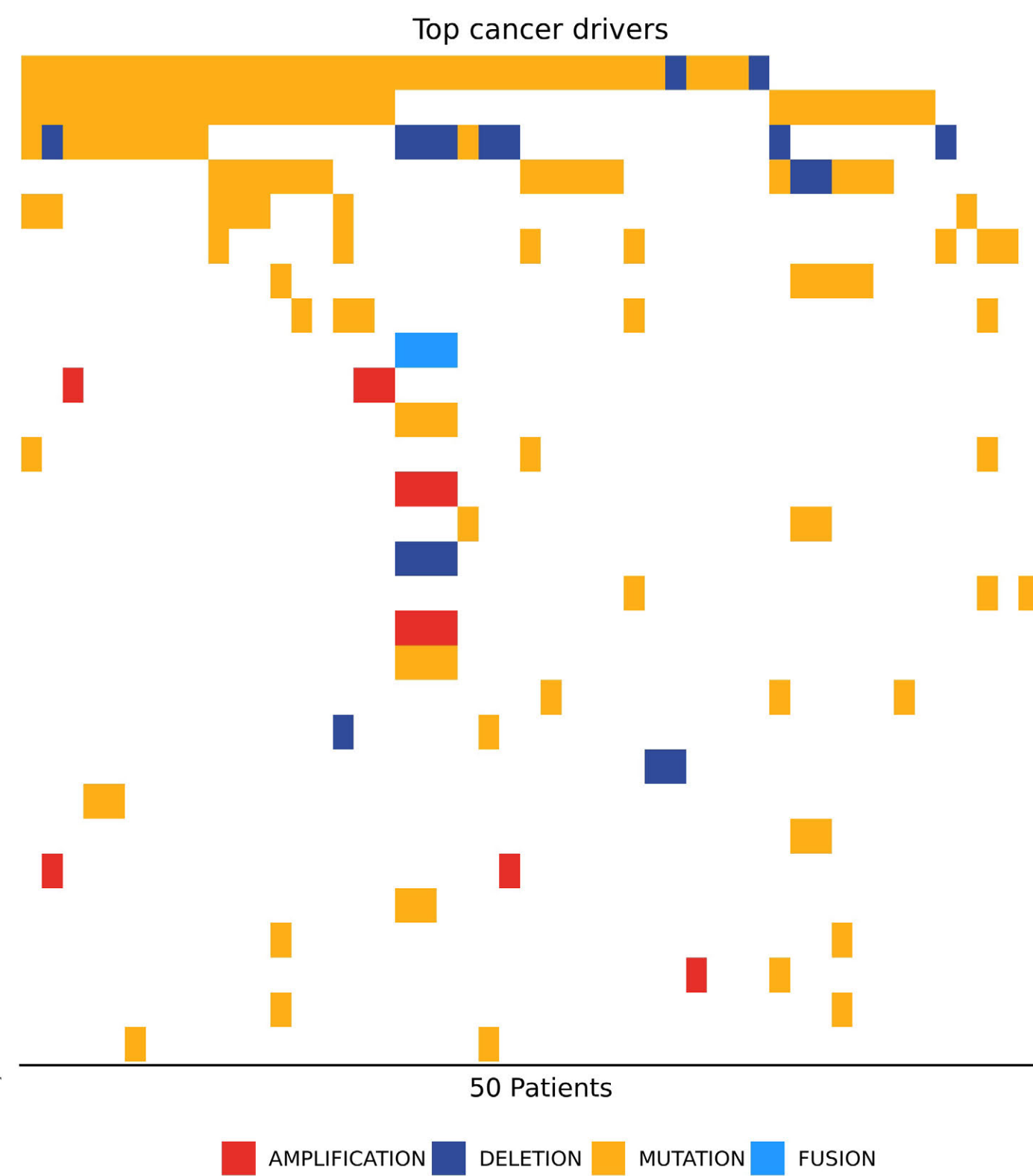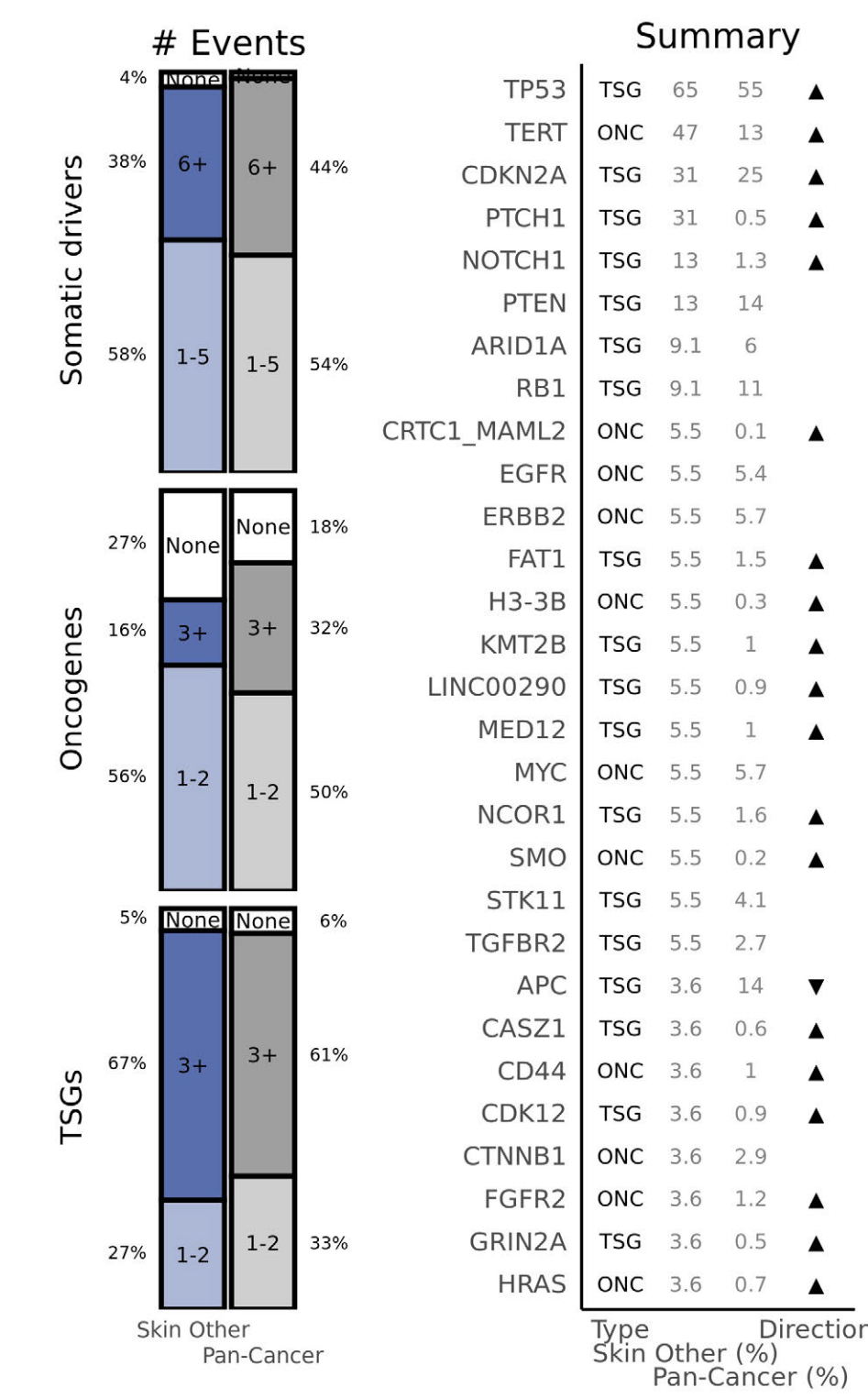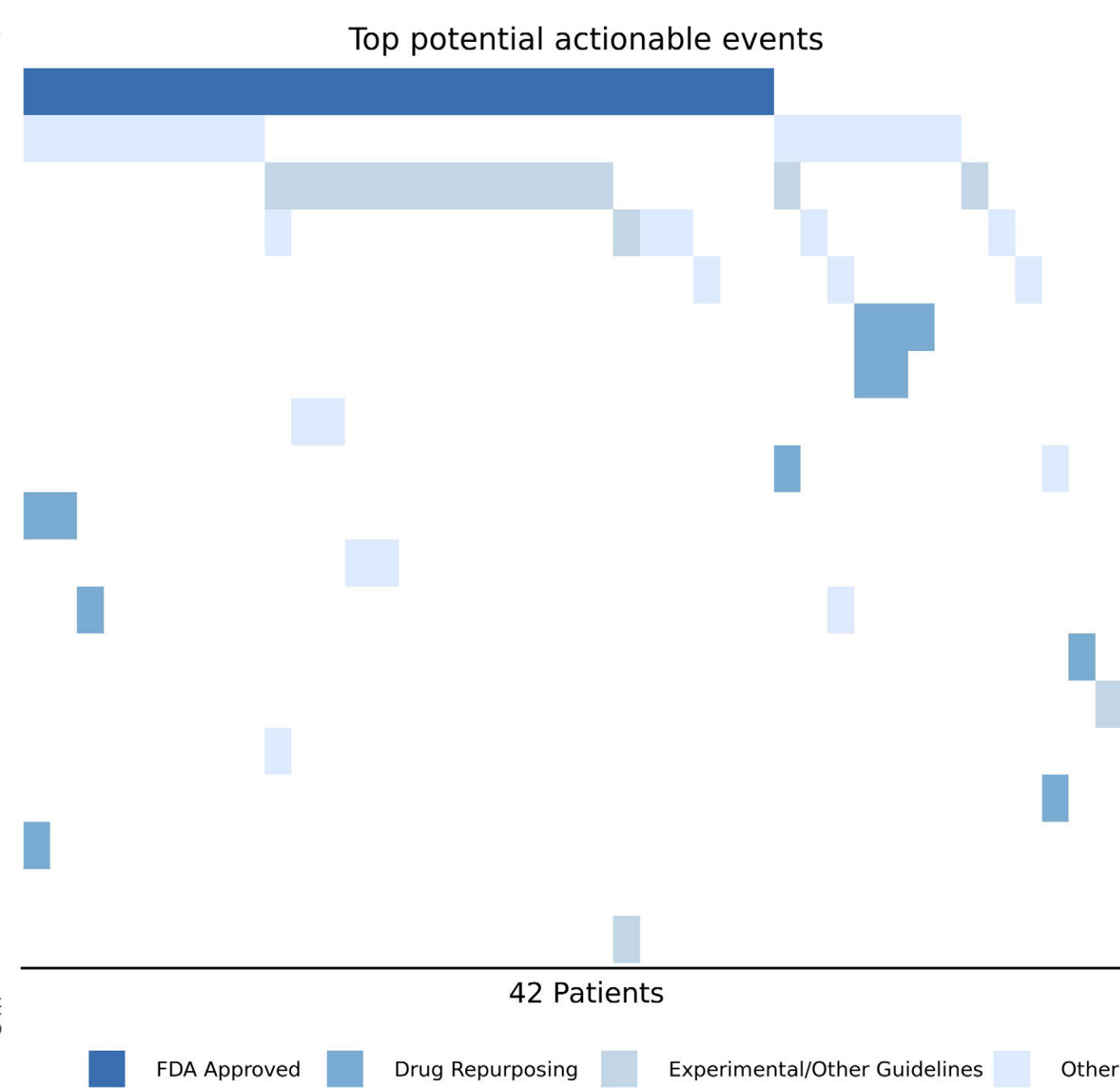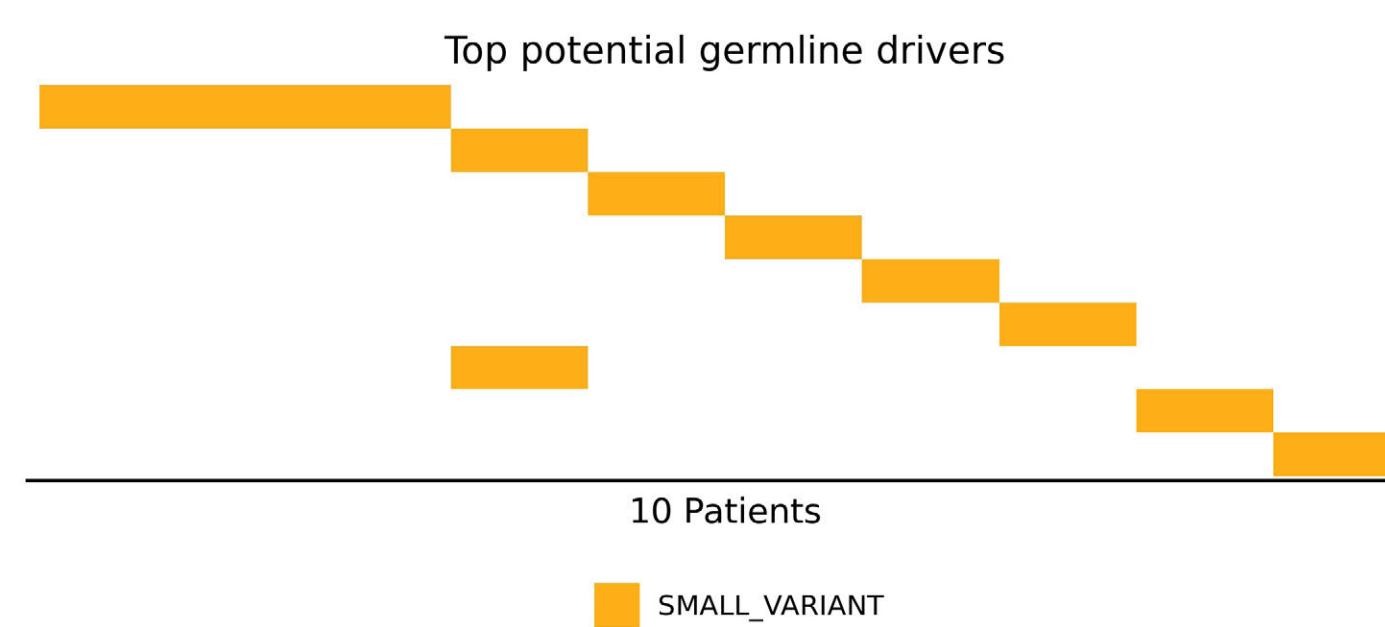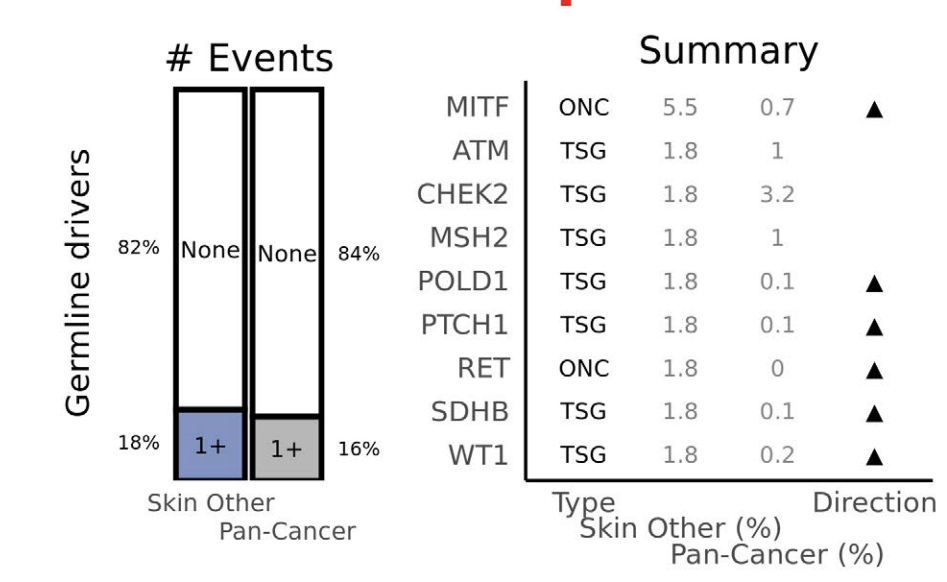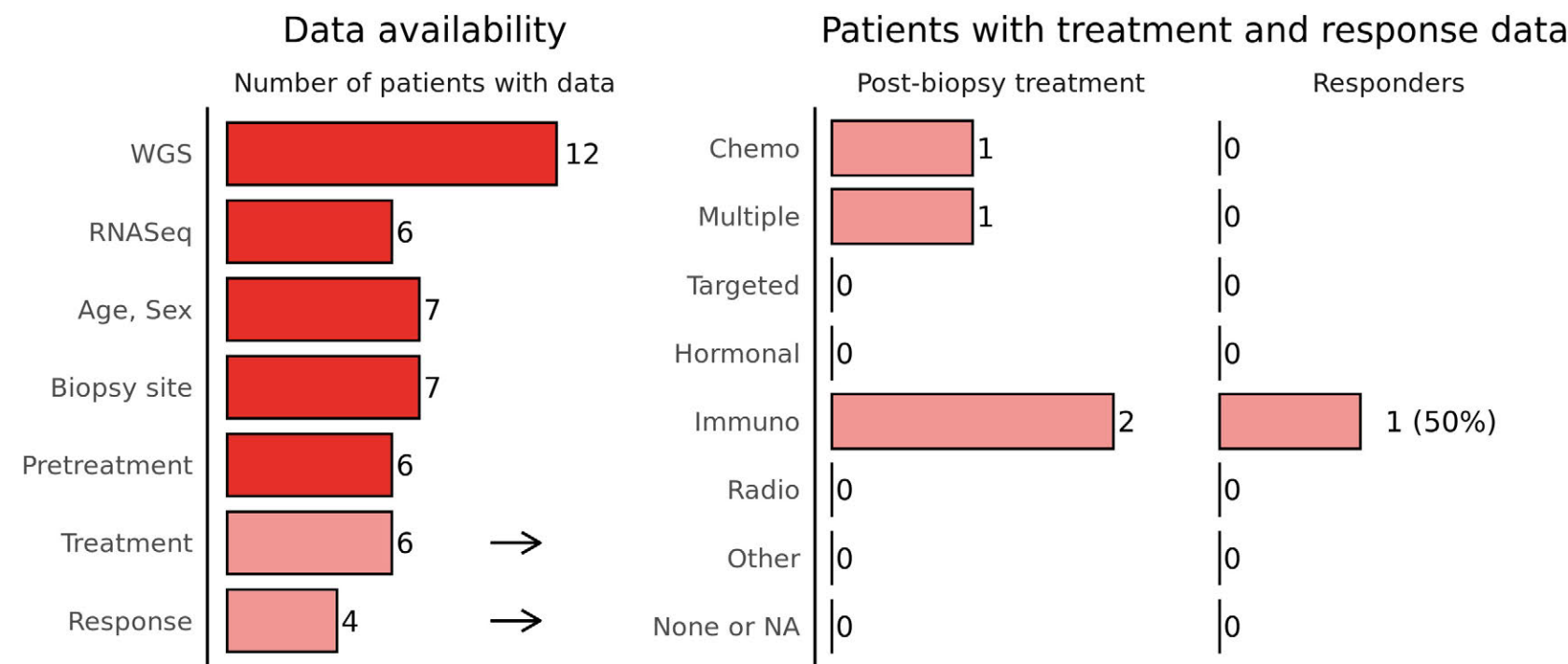Date created from database: 2024-07-06

# The Genomic And Actionability Landscape Of Melanoma

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability
**Number of patients with data**

| | |
|---|---|
| WGS | 313 |
| RNASeq | 232 |
| Age, Sex | 280 |
| Biopsy site | 277 |
| Pretreatment | 279 |
| Treatment | 260 |
| Response | 225 |

### Patients with treatment and response data

| Post-biopsy treatment | Responders |
|---|---|
| Chemo — 4 | 0 |
| Multiple — 7 | 3 (43%) |
| Targeted — 40 | 31 (78%) |
| Hormonal — 0 | 0 |
| Immuno — 183 | 77 (42%) |
| Radio — 42 | 13 (31%) |
| Other — 1 | 0 |
| None or NA — 0 | 0 |

## Tumor Characteristics

Melanoma | Pan-Cancer

| | TMB High | MSI High | WGD | Diploid Proportion | GIE HLA LOH | GIE Overall | Viral Insertions | HRD |
|---|---|---|---|---|---|---|---|---|
| Melanoma | 72% | 0% | 46% | 39% | 10% | 21% | 0% | 0% |
| Pan-Cancer | 21% | 2% | 56% | 34% | 19% | 26% | 3% | 6% |

## Mutational Landscape

### Tumor purity
62% / 55%

### Clonal mutation fraction
98% / 95%

### Tumor mutational burden
19 (72%) / 4 (21%) — High — TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Melanoma | 51,488 | 726 | 115 | 959 |
| Pan-Cancer | 10,846 | 983 | 183 | 92 |

Number of variants — Quantile

### Telomere Length
0.89 / 0.82 — Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
10 / 6 — Log2 (CDR3 + 1)

### Microsatellite instability
0.1 (0%) / 0.15 (2%) — Instable — MS indels per megabase

### Mean genome ploidy
2.2 / 2.6

### Aneuploidy Score
12 / 16

### % Copy number alteration
41% / 54%

### % Genome LOH
22% / 24%

## Processes Underlying Mutations

- UV light: 89%
- DNA damage repair: 3%
- Chemical exposure: 1%
- APOBEC: 1%
- Ageing: 0%
- Tobacco: 0%
- Unknown: 6%

Melanoma 313 Patients — Pan-Cancer 6790 Patients — Skin

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## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

| Gene | Type | Melanoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TERT | ONC | 76 | 13 | ▲ |
| CDKN2A | TSG | 54 | 25 | |
| BRAF | ONC | 51 | 6.2 | ▲ |
| NRAS | ONC | 28 | 2.8 | ▲ |
| PTEN | TSG | 23 | 14 | |
| TP53 | TSG | 16 | 55 | ▼ |
| NF1 | TSG | 8 | 11 | |
| MAP2K1 | ONC | 6.7 | 0.9 | ▲ |
| APC | TSG | 4.8 | 14 | ▼ |
| RB1 | TSG | 4.8 | 11 | ▼ |
| ARID2 | TSG | 4.5 | 1.8 | |
| IDH1 | ONC | 4.2 | 1.3 | ▲ |
| RAC1 | ONC | 4.2 | 0.5 | ▲ |
| B2M | TSG | 3.5 | 1.9 | |
| CCND1 | ONC | 3.5 | 5.6 | |
| KMT2B | TSG | 3.5 | 1 | |
| PIK3CA | ONC | 3.5 | 13 | ▼ |
| PPP6C | ONC | 3.5 | 0.3 | ▲ |
| FGF3 | ONC | 3.2 | 5.2 | |
| PBRM1 | TSG | 3.2 | 3.2 | |
| ZBTB10 | ONC | 3.2 | 2.1 | |
| CDK4 | ONC | 2.6 | 2 | |
| CYLD | TSG | 2.6 | 1.9 | |
| KIT | ONC | 2.6 | 1.8 | |
| MYC | ONC | 2.6 | 5.7 | |
| TSC1 | ONC | 2.6 | 1.1 | |
| BAP1 | TSG | 2.2 | 2.7 | |
| CTNNB1 | ONC | 2.2 | 2.9 | |
| NCOA2 | ONC | 2.2 | 1.6 | |

Somatic drivers: 23% 6+ / 44% 6+; 77% 1-5 / 54% 1-5
Oncogenes: 35% 3+ / 18% 3+; 63% 1-2 / 50% 1-2
TSGs: 8% None / 6% None; 33% 3+ / 61% 3+; 59% 1-2 / 33% 1-2

Top cancer drivers — 308 Patients

Legend: **AMPLIFICATION** · **DELETION** · **MUTATION**

## Potentially Actionable Events

### # Events / Summary

| Gene | Melanoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| TMB High | 72 | 21 | ▲ |
| CDKN2A | 54 | 24 | ▲ |
| BRAF | 50 | 5.9 | ▲ |
| NRAS | 28 | 2.6 | ▲ |
| PTEN | 23 | 13 | ▲ |
| MAP2K1 | 6.7 | 0.8 | ▲ |
| CHEK2 | 4.2 | 3 | |
| IDH1 | 4.2 | 1 | ▲ |
| PIK3CA | 3.5 | 13 | ▼ |
| CCND1 | 3.2 | 5.3 | |
| TSC1 | 2.6 | 1.1 | |
| CDK4 | 2.2 | 1.9 | |
| CTNNB1 | 2.2 | 2.7 | |
| KIT | 2.2 | 1.1 | |
| ATM | 1.3 | 3.5 | |
| EZH2 | 1.3 | 0.2 | ▲ |
| BRCA2 | 1 | 2.4 | |
| ERBB2 | 1 | 5.6 | ▼ |
| HRAS | 1 | 0.6 | |
| IGF1R | 1 | 0.4 | |
| KRAS | 1 | 14 | ▼ |
| AGK - BRAF fusion | 0.6 | 0.1 | ▲ |
| ARAF | 0.6 | 0.1 | ▲ |
| Rest FDA | 0.3 | | |
| Rest Repurpose | 6.4 | | |
| Rest Experimental | 0.6 | | |
| Rest Other | 2.9 | | |

Actionable: 4% None / 18% None; 61% 3+ / 26% 3+; 34% 1-2 / 56% 1-2
Best treatment option: 4% None / 18% None; 4% Oth / 14% Oth; Exp 5%; 88% FDA / 28% Off; 36% FDA

Top potential actionable events — 299 Patients

Legend: **FDA Approved** · **Drug Repurposing** · **Experimental/Other Guidelines** · **Other**

## Germline Predisposition

### # Events / Summary

| Gene | Type | Melanoma (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 4.2 | 3.2 | |
| MUTYH | TSG | 2.9 | 1.9 | |
| MITF | ONC | 1.9 | 0.7 | |
| MSH2 | TSG | 1.6 | 1 | |
| BRCA2 | TSG | 1.3 | 1.5 | |
| CDKN2A | TSG | 1.3 | 0.2 | ▲ |
| SDHA | TSG | 1 | 0.5 | |
| BRCA1 | TSG | 0.6 | 1.1 | |
| APC | TSG | 0.3 | 0.2 | |

Germline drivers: 84% None / 84% None; 16% 1+ / 16% 1+

Top potential germline drivers — 45 Patients

Legend: **STRUCTURAL_VARIANT** · **SMALL_VARIANT**

## WGS vs Panel Coverage

Legend: **FDA Approved** · **Drug Repurposing** · **Other** · **None**

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA | Repurpose | Other |
|---|---|---|---|
| WGS | 274 | 13 | 12 |
| Comprehensive 521 gene panel | 274 | 10 | 16 |
| Targeted 50 gene panel | 240 | 18 | 40 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 1.5 | 0.36 | 0.28 | 0.88 | 3 |
| Comprehensive 521 gene panel | 1.5 | 0.31 | 0.69 | | 2.7 |
| Targeted 50 gene panel | 0.77 | 0.56 | | | 1.5 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: (none significant)
Drug Repurposing: Fusion 12; Partial CN Loss 3; HRD 1
Experimental/Other Guidelines: Partial CN Loss 29; Small Variant 1; Partial CN Gain 1
Other: Partial CN Loss 34; Full CN Loss 14; HMZ Disruption 11; Small Variant 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 224
Drug Repurposing: Small Variant 57; Fusion 12; Partial CN Loss 3; Splice Site 3; HRD
Experimental/Other Guidelines: Partial CN Loss 29; Full CN Gain 25; Small Variant 8; Full CN Loss 1; Partial CN Gain 1
Other: Partial CN Loss 34; Small Variant 29; Full CN Loss 16; HMZ Disruption 11; Splice Site 10

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the % of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red), moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: SKCM
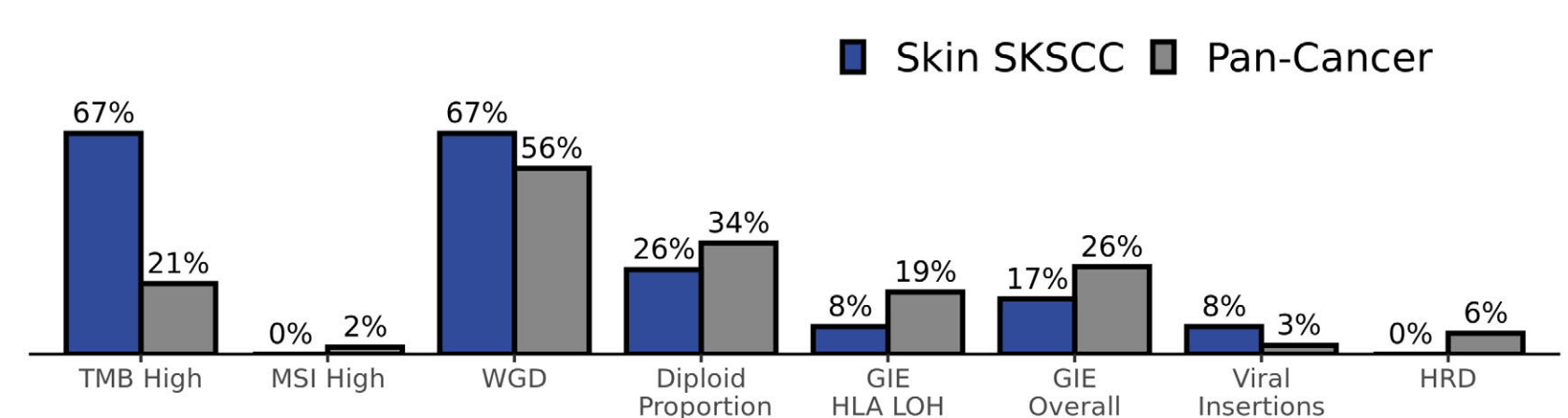DOIDs included: 8923
Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
- Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
- Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
- Other events: Fusions, HMZ (homozygous) Distruptions, HLA Insers, HLA assumed not captured by panels.
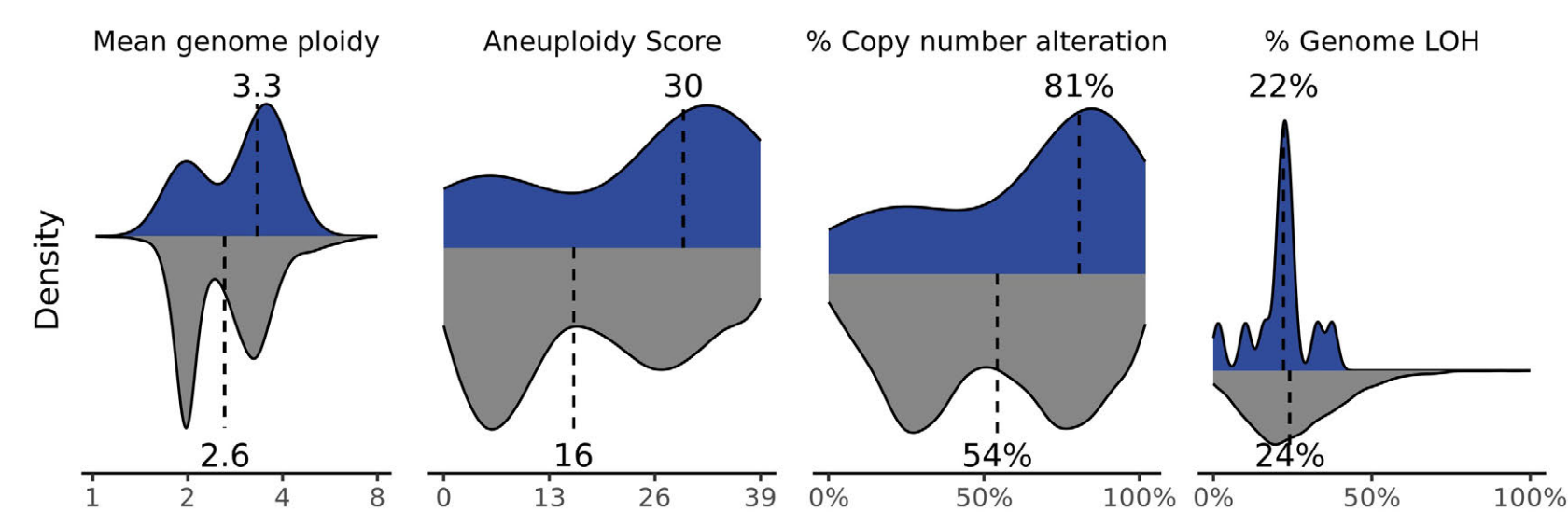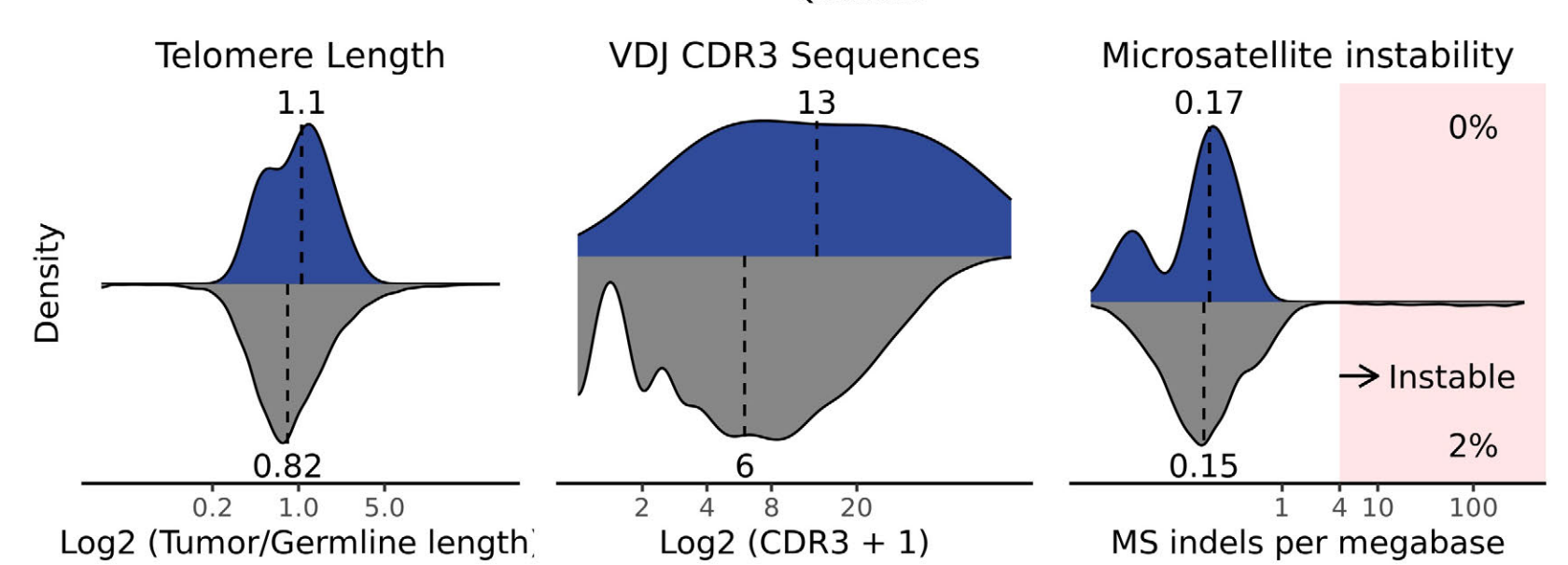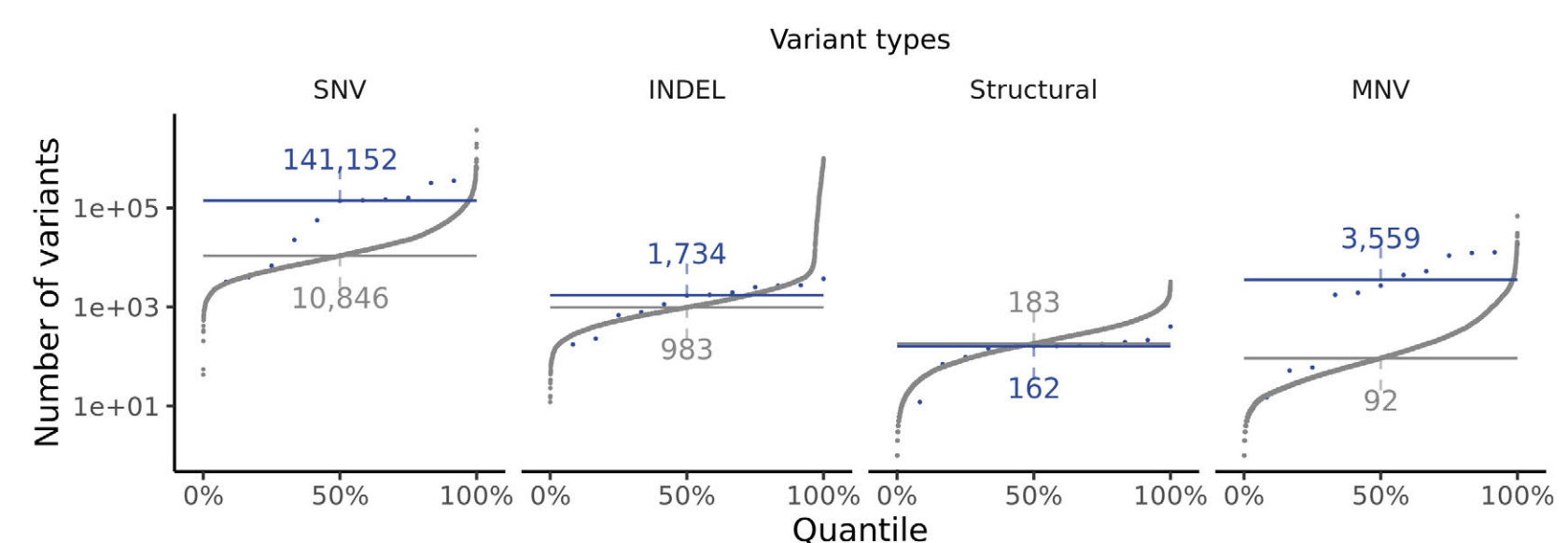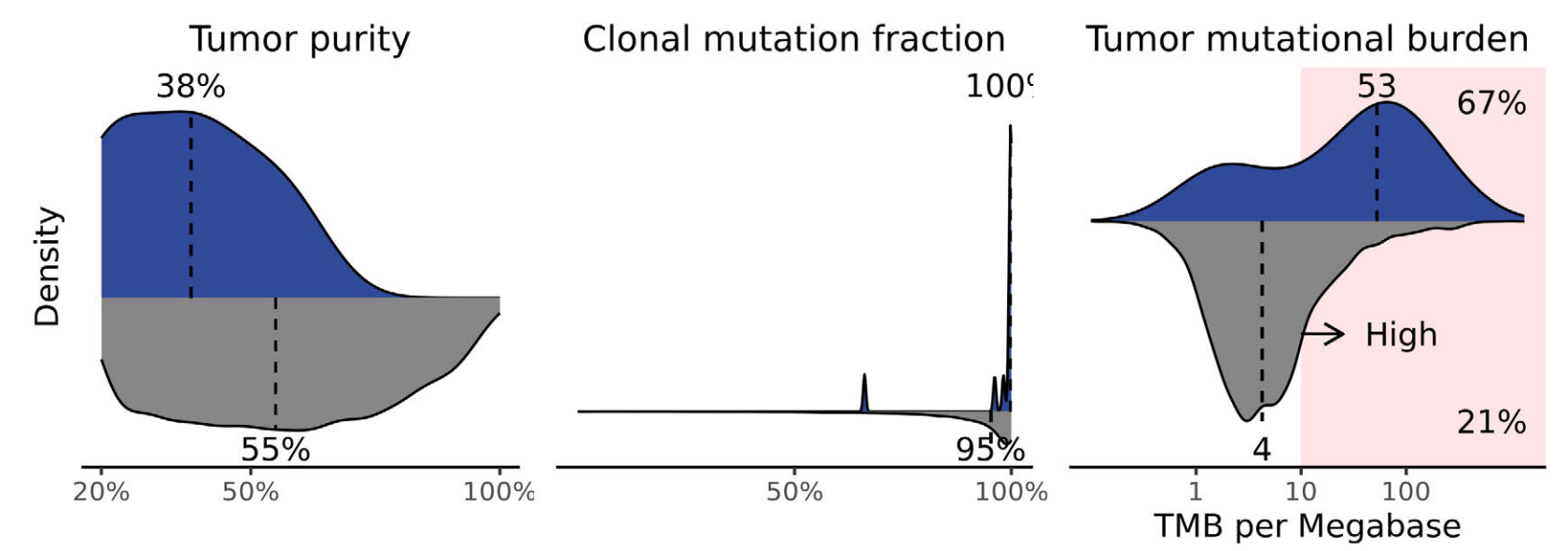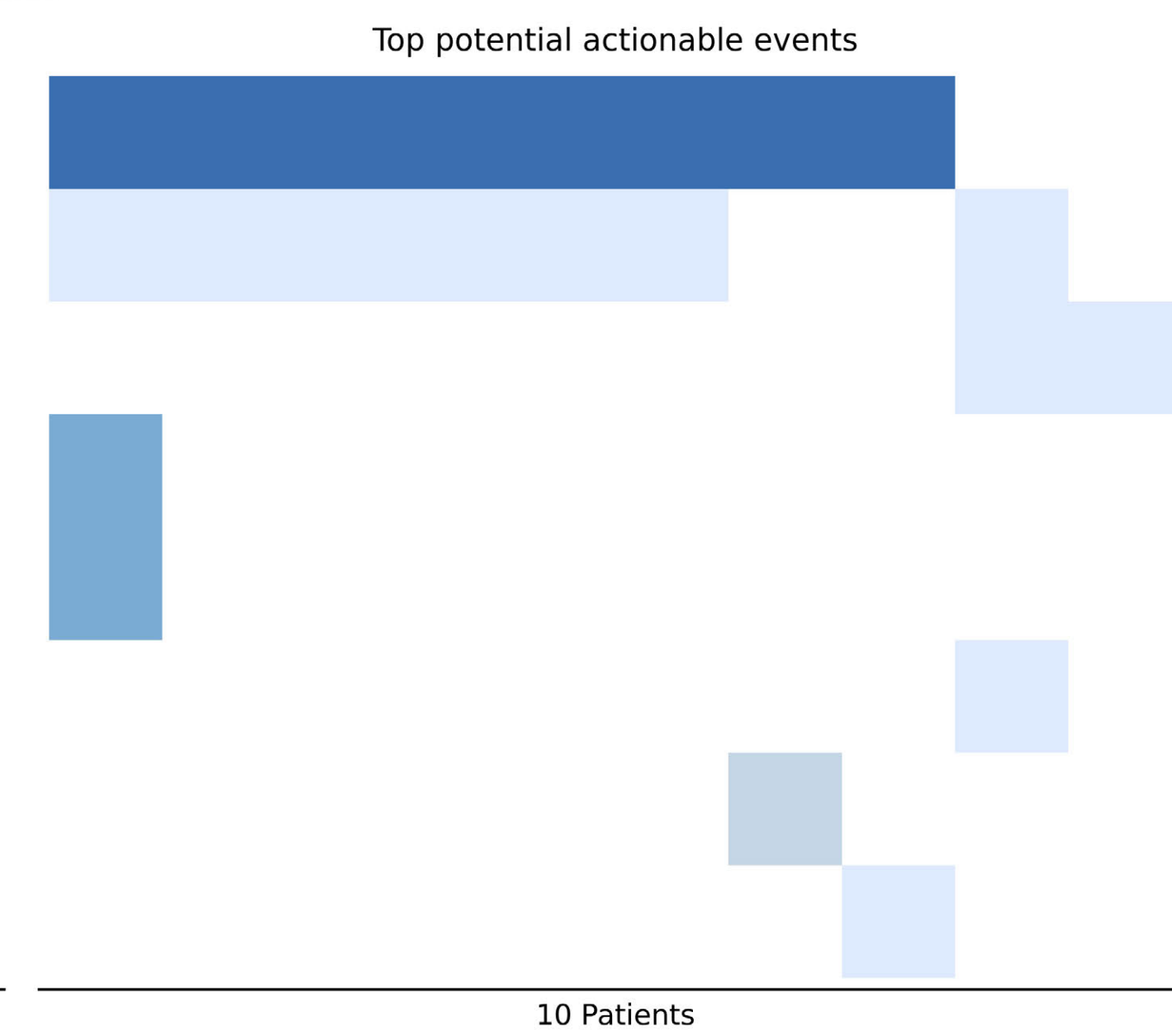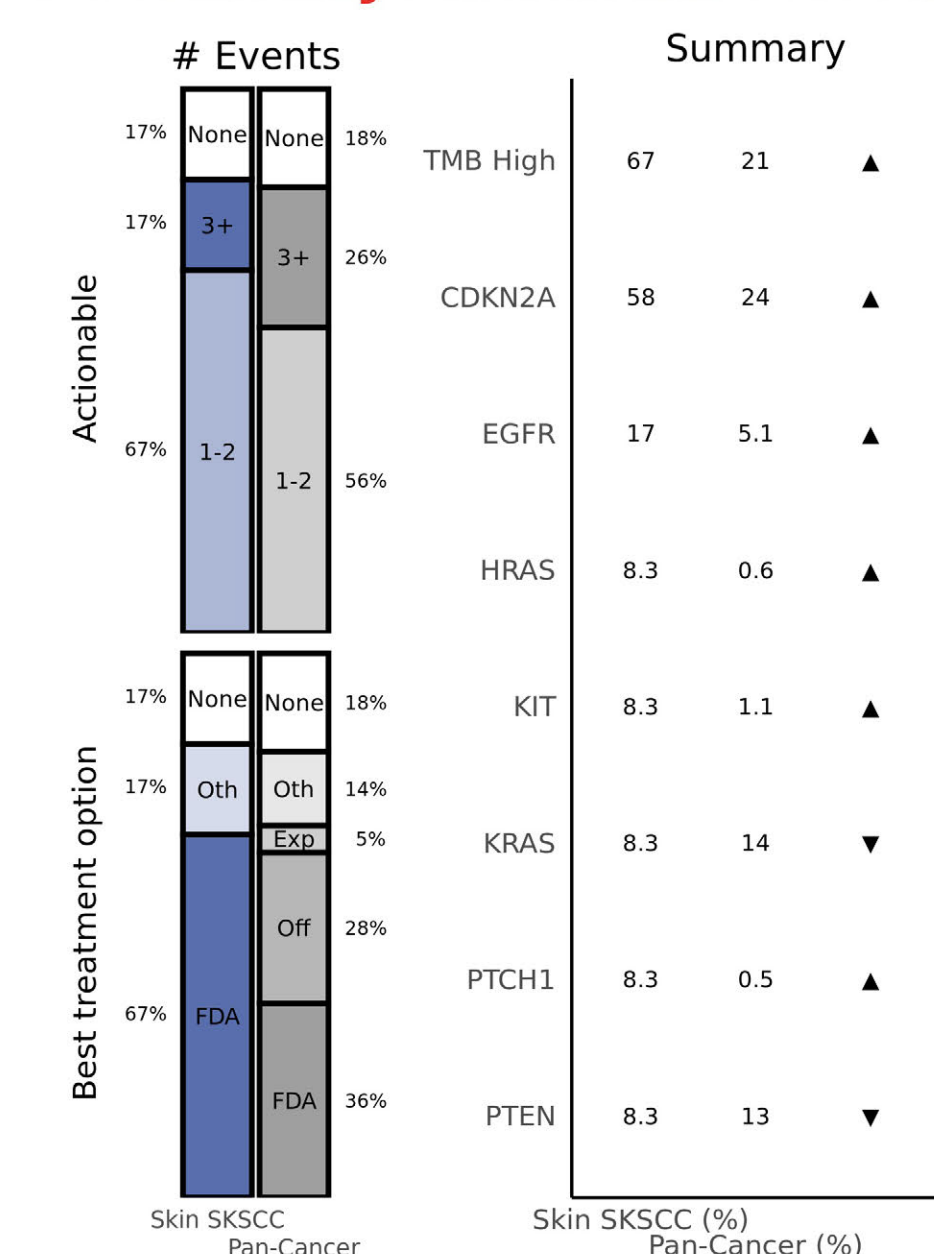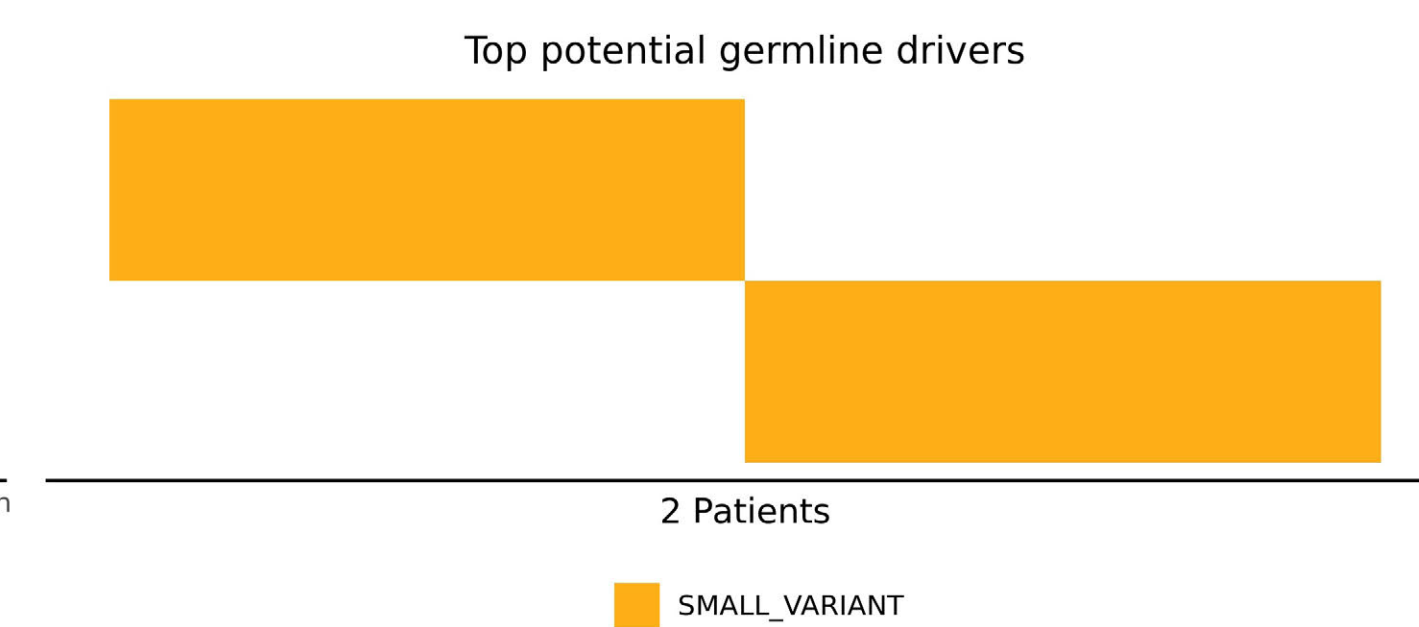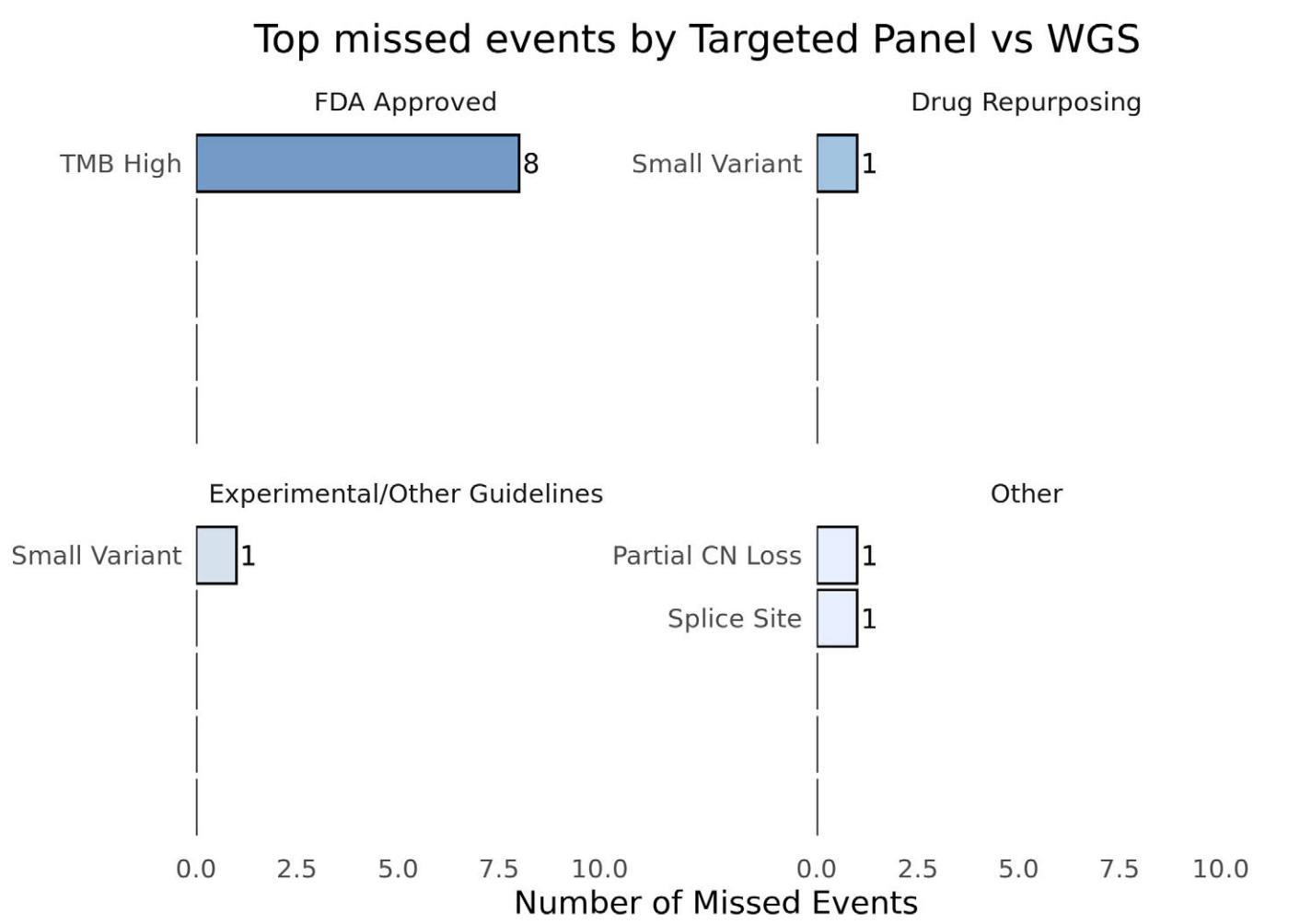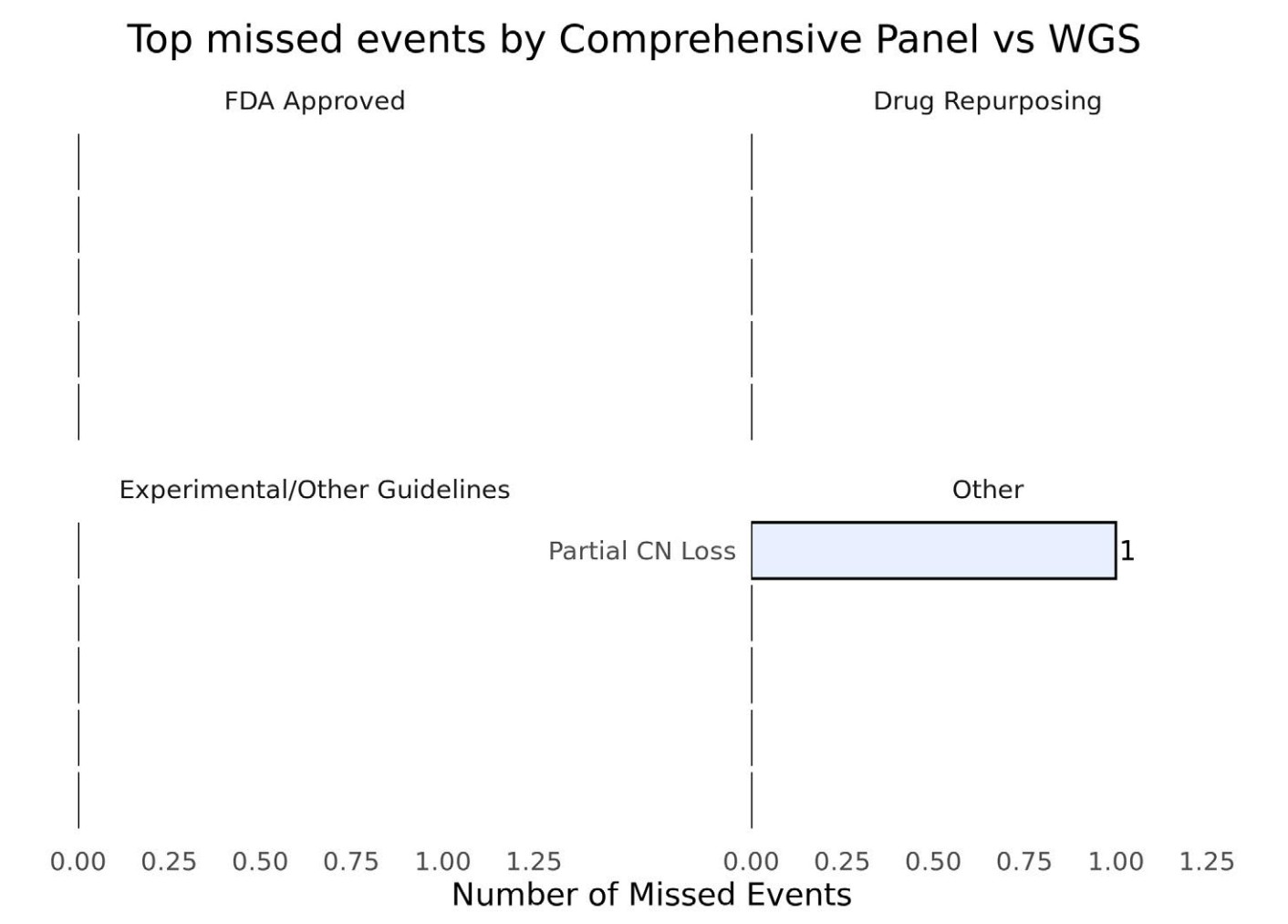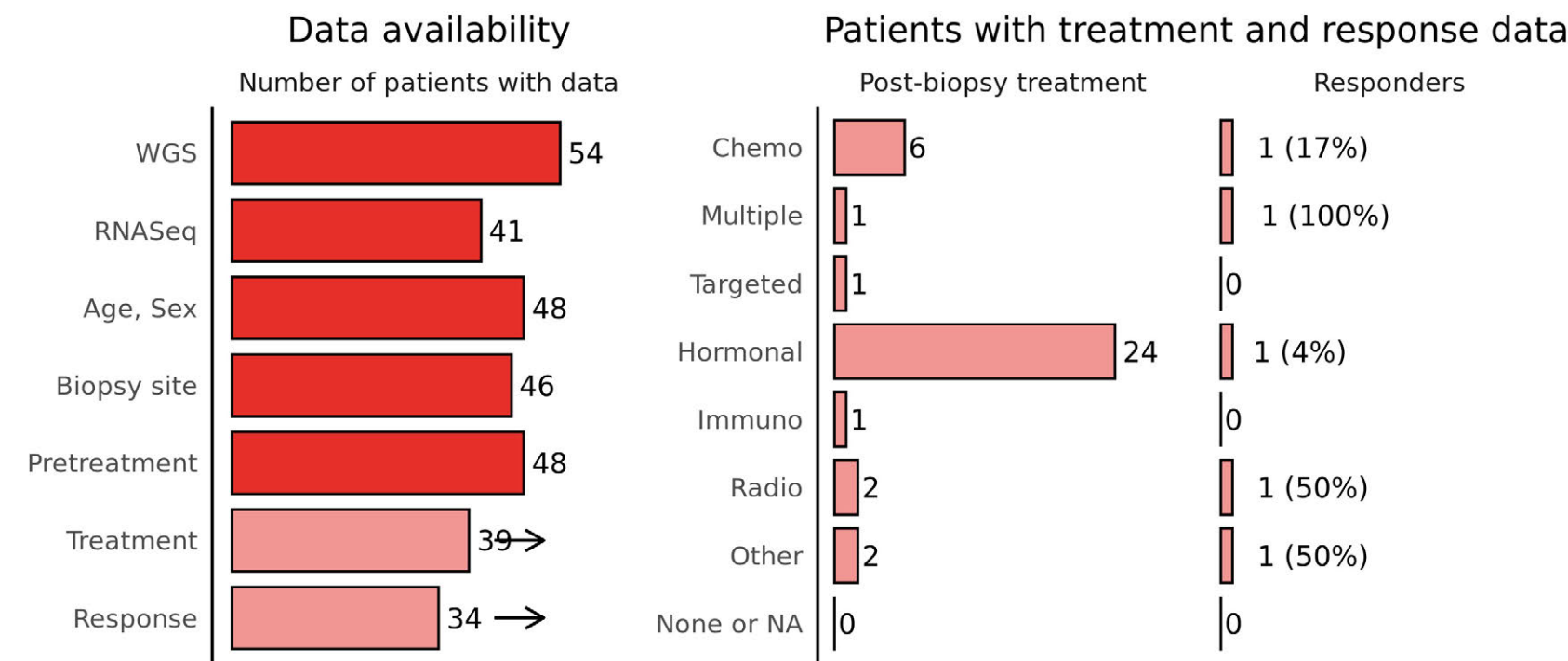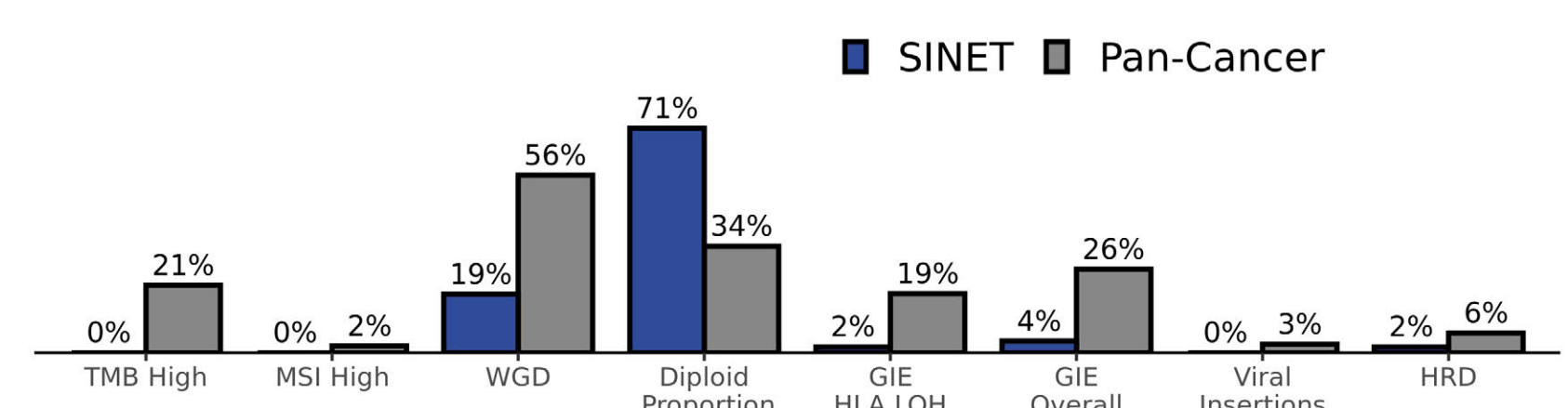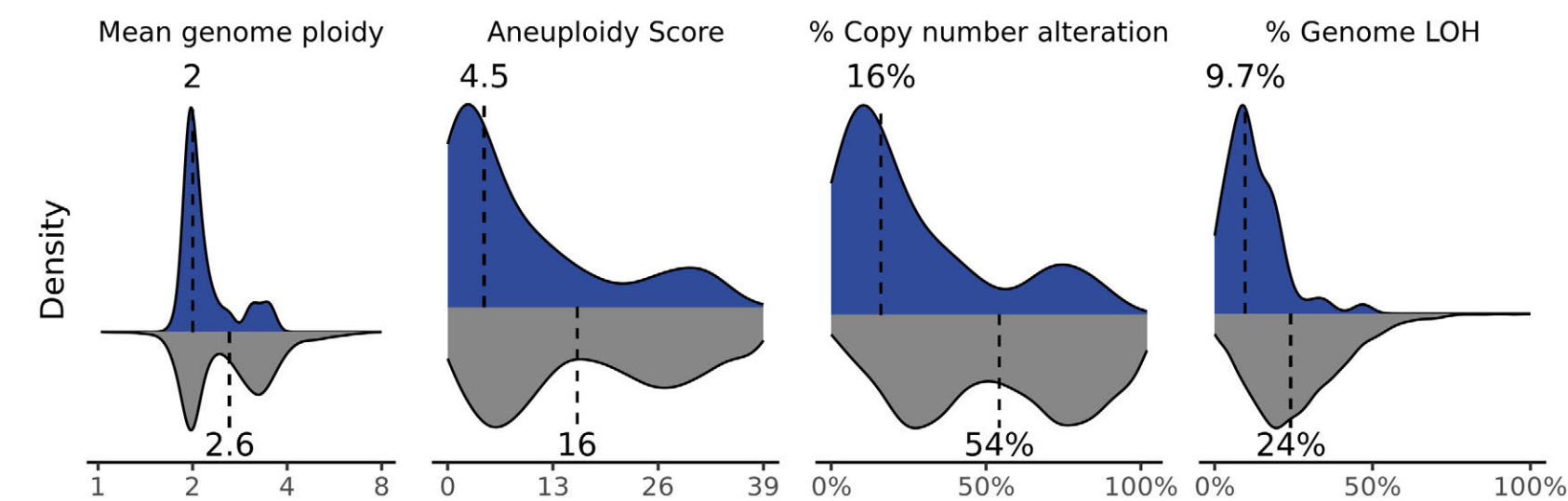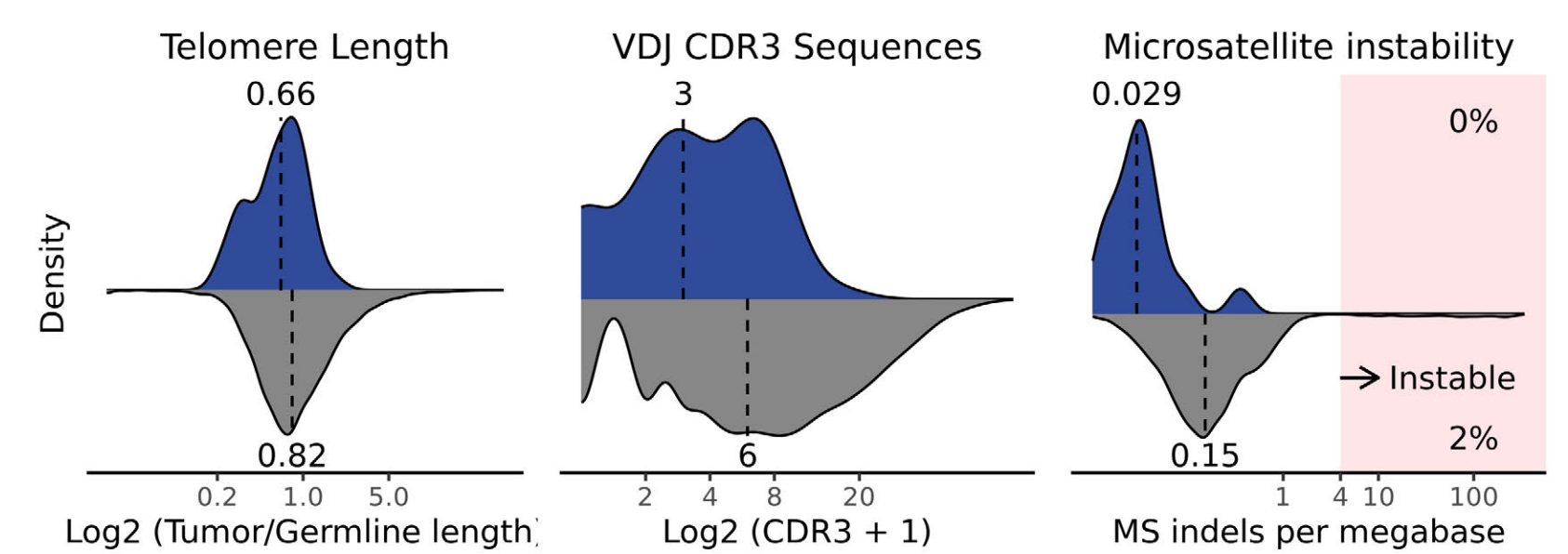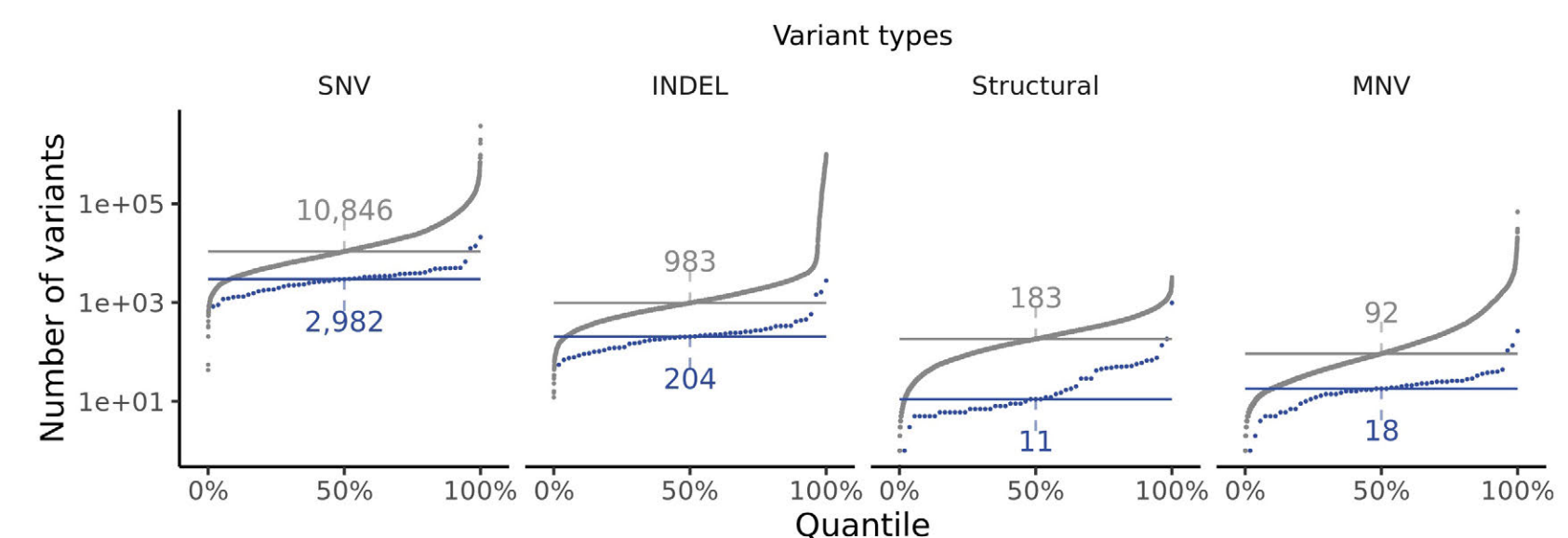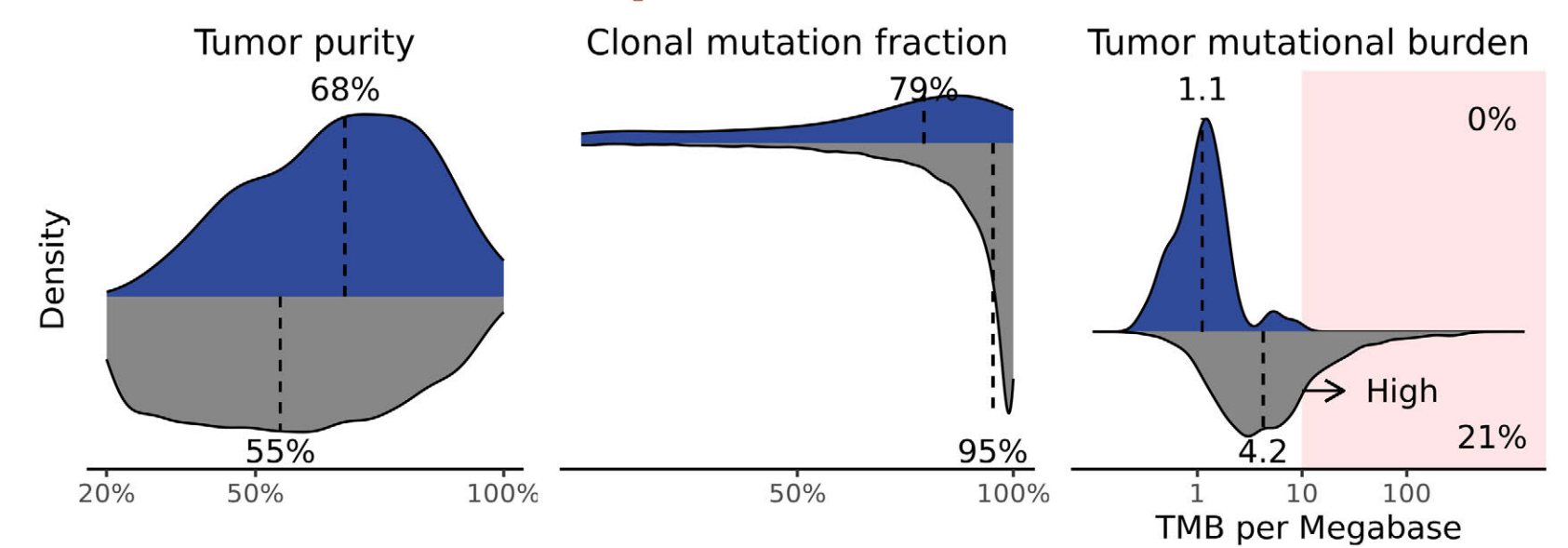** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Skin Non-Melanoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 55 |
| RNASeq | 22 |
| Age, Sex | 26 |
| Biopsy site | 23 |
| Pretreatment | 19 |
| Treatment | 16 → |
| Response | 12 → |

**Patients with treatment and response data**

Post-biopsy treatment / Responders

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 4 | 2 (50%) |
| Multiple | 1 | 0 |
| Targeted | 4 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 3 | 1 (33%) |
| Radio | 3 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | |

## Tumor Characteristics

Legend: Skin Other (dark blue), Pan-Cancer (gray)

| | Skin Other | Pan-Cancer |
|---|---|---|
| TMB High | 57% | 21% |
| MSI High | 0% | 2% |
| WGD | 35% | 56% |
| Diploid Proportion | 53% | 34% |
| GIE HLA LOH | 19% | 19% |
| GIE Overall | 30% | 26% |
| Viral Insertions | 17% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

**Tumor purity** — 54% / 55%

**Clonal mutation fraction** — 98% / 95%

**Tumor mutational burden** — 16 / 57% High; 4 / 21%; TMB per Megabase

**Variant types**

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Skin Other | 43,885 | 1,128 | 183 | 1,933 |
| Pan-Cancer | 10,846 | 983 | 152 | 92 |

Number of variants vs Quantile

**Telomere Length** — 1 / 0.82; Log2 (Tumor/Germline length)

**VDJ CDR3 Sequences** — 8 / 6; Log2 (CDR3 + 1)

**Microsatellite instability** — 0.15 / 0% ; 0.15 / 2% → Instable; MS indels per megabase

**Mean genome ploidy** — 2.1 / 2.6

**Aneuploidy Score** — 7 / 16

**% Copy number alteration** — 22% / 54%

**% Genome LOH** — 16% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| UV light: | 83% |
| APOBEC: | 4% |
| Chemical exposure: | 3% |
| DNA damage repair: | 1% |
| Ageing: | 0% |
| Tobacco: | 0% |
| Unknown: | 7% |

**Skin Other** 55 Patients

**Pan-Cancer** 6790 Patients

Skin

Made with bioRender
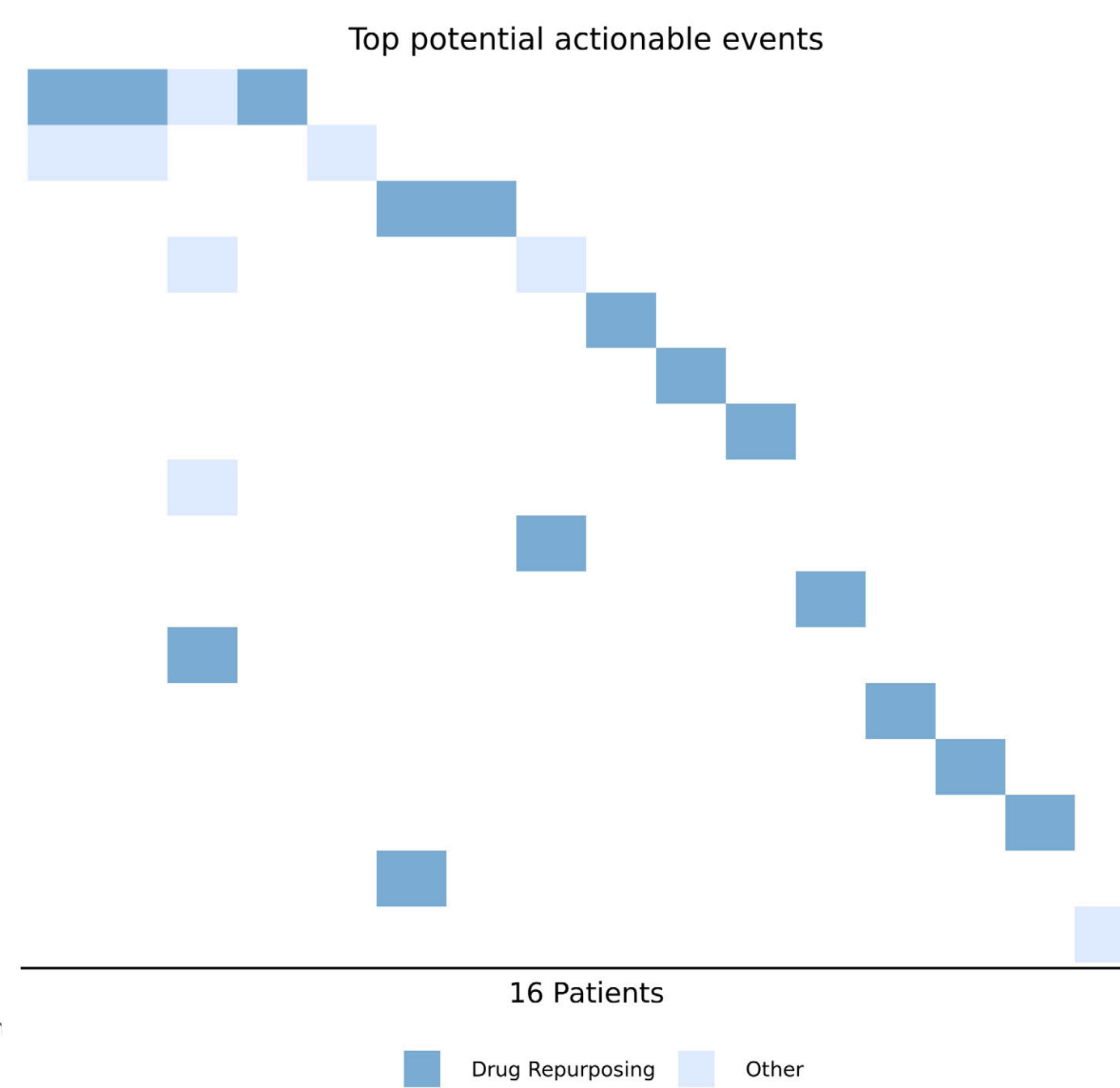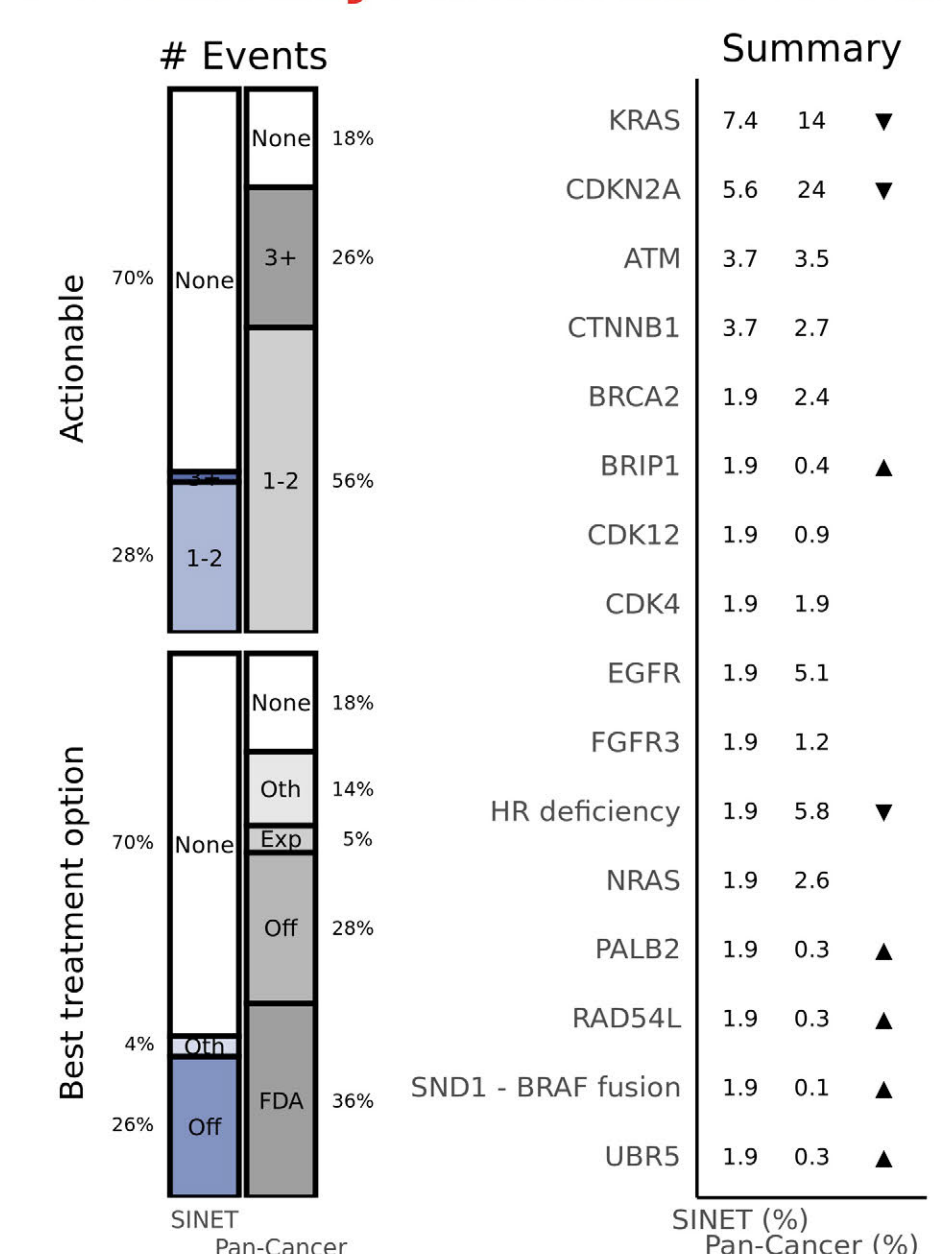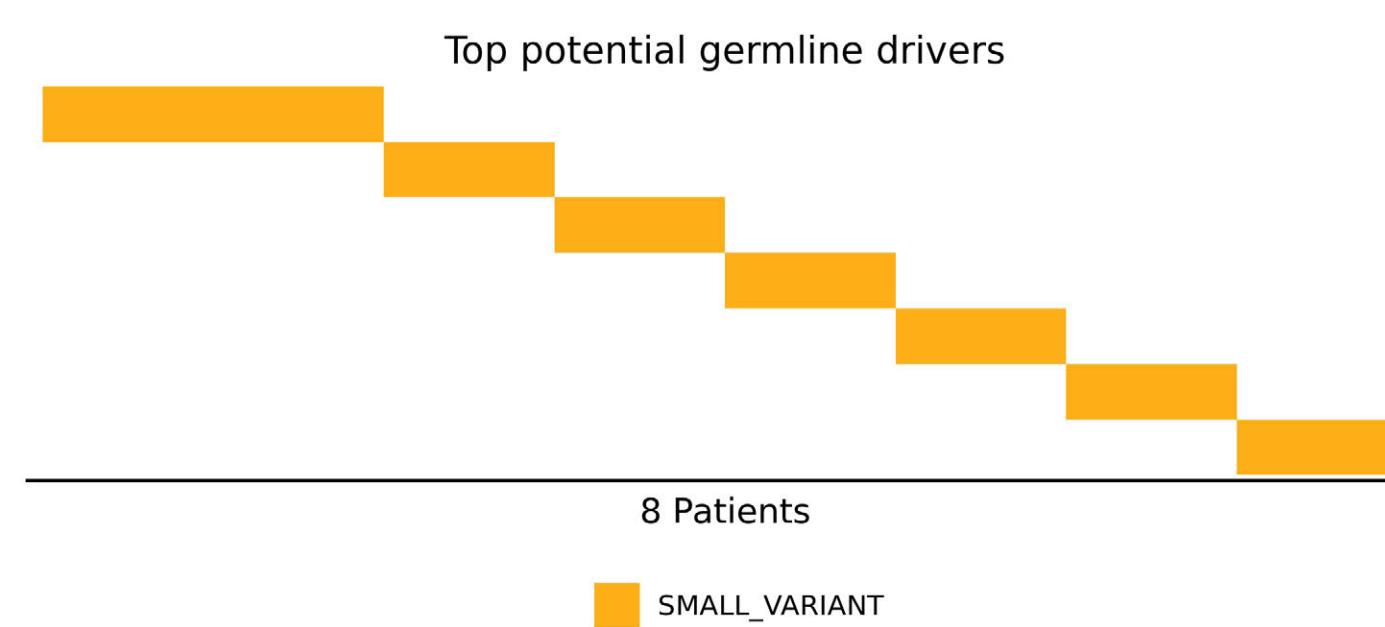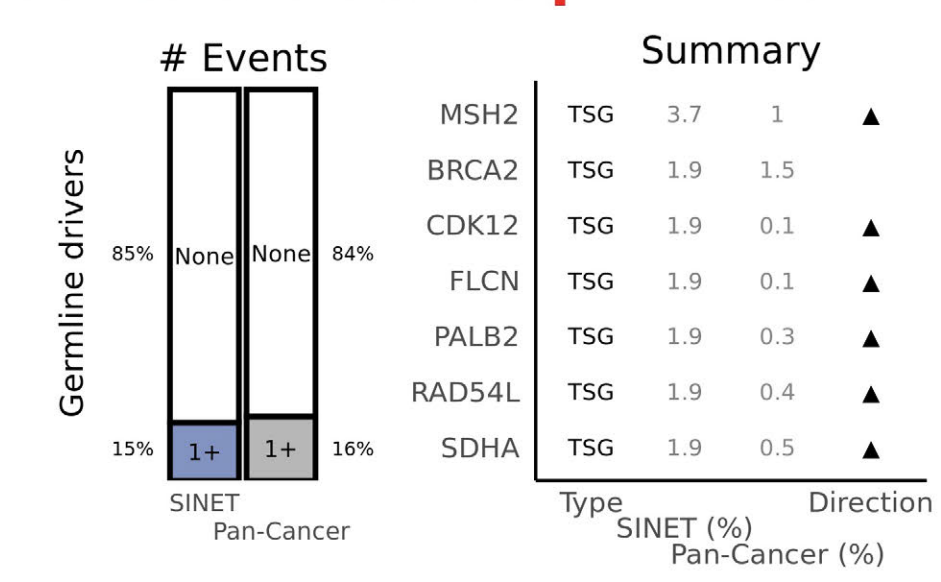
## Copy Number Alteration Profile



## Cancer Driver Landscape

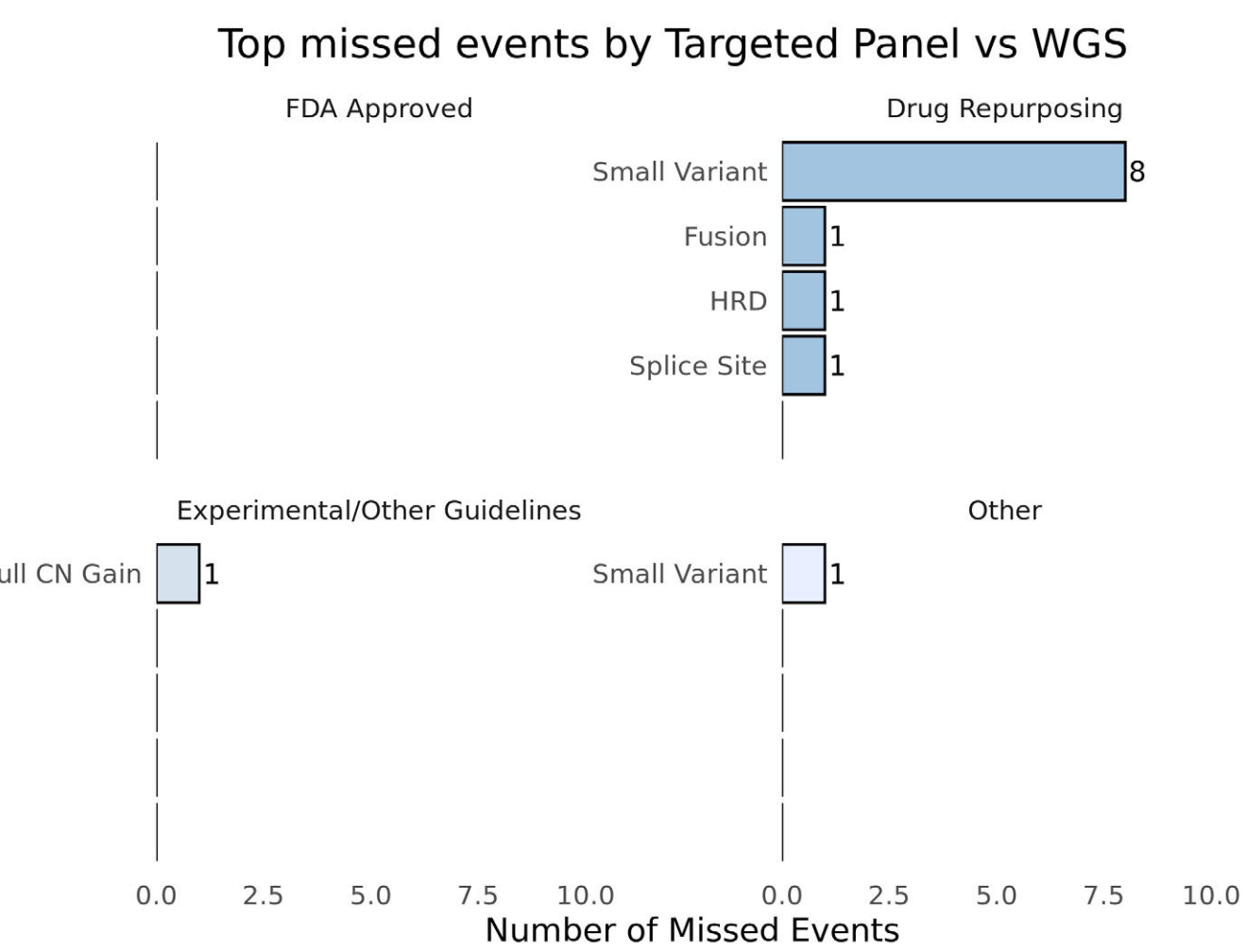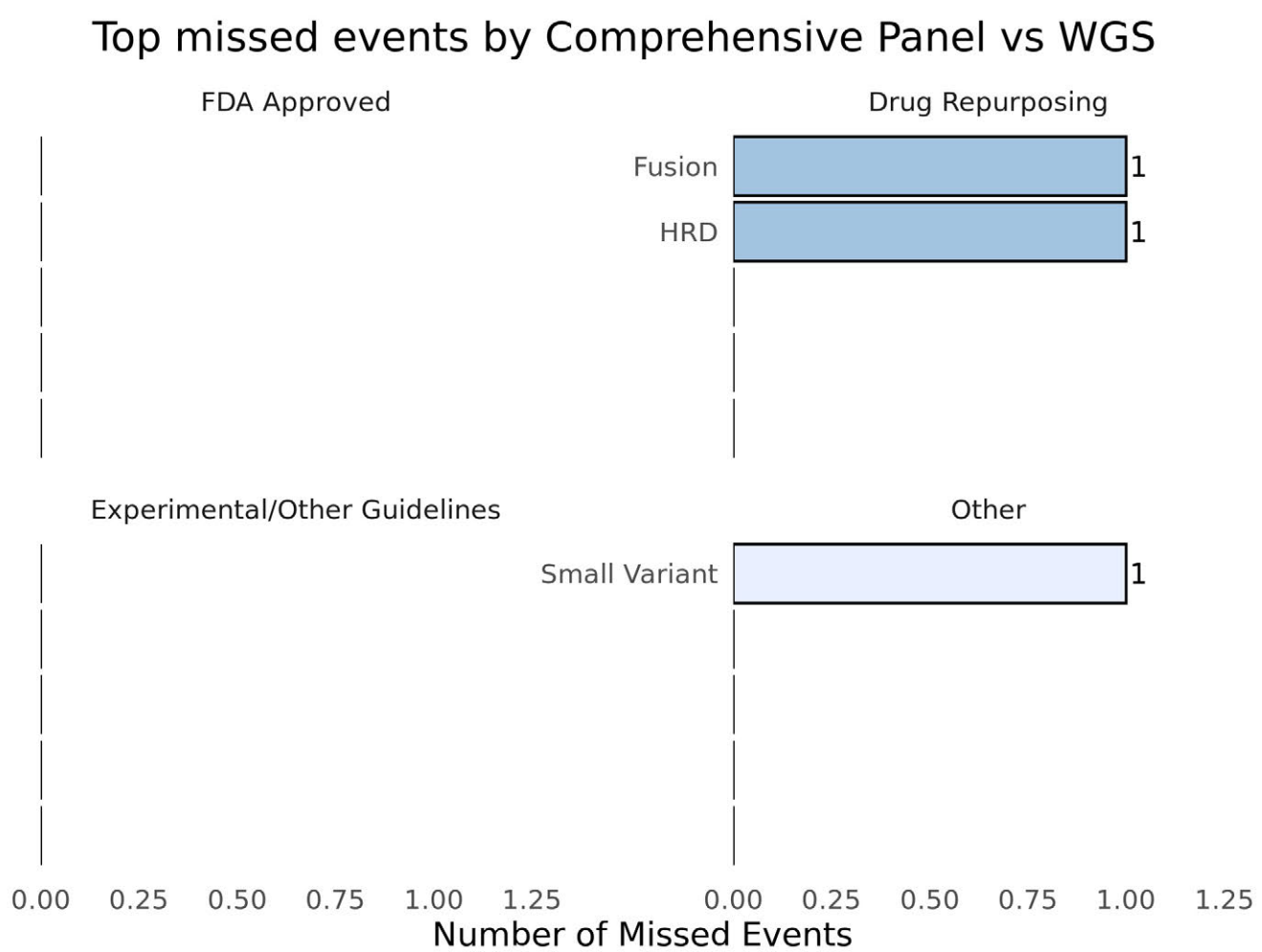### # Events / Summary

| | | | Type | Skin Other % | Pan-Cancer % | Dir |
|---|---|---|---|---|---|---|
| Somatic drivers | | | TP53 | TSG | 65 | 55 ▲ |
| | | | TERT | ONC | 47 | 13 ▲ |
| | | | CDKN2A | TSG | 31 | 25 ▲ |
| | | | PTCH1 | TSG | 31 | 0.5 ▲ |
| Oncogenes | | | NOTCH1 | TSG | 31 | 1.3 ▲ |
| | | | PTEN | TSG | 13 | 14 |
| | | | ARID1A | TSG | 9.1 | 6 |
| | | | RB1 | TSG | 9.1 | 11 |
| | | | CRTC1_MAML2 | ONC | 5.5 | 0.1 ▲ |
| | | | EGFR | ONC | 5.5 | 5.4 |
| | | | ERBB2 | ONC | 5.5 | 5.7 |
| | | | FAT1 | TSG | 5.5 | 1.5 |
| | | | H3-3B | TSG | 5.5 | 0.3 ▲ |
| | | | KMT2B | TSG | 5.5 | 1 |
| | | | LINC00290 | TSG | 5.5 | 0.9 ▲ |
| | | | MED12 | TSG | 5.5 | 1 ▲ |
| | | | MYC | ONC | 5.5 | 5.7 |
| | | | NCOR1 | TSG | 5.5 | 1.6 ▲ |
| | | | SMO | ONC | 5.5 | 0.2 ▲ |
| | | | STK11 | TSG | 5.5 | 4.1 |
| TSGs | | | TGFBR2 | TSG | 5.5 | 2.7 |
| | | | APC | TSG | 3.6 | 14 ▼ |
| | | | CASZ1 | TSG | 3.6 | 0.6 ▲ |
| | | | CD44 | ONC | 3.6 | 1 ▲ |
| | | | CDK12 | TSG | 3.6 | 0.9 ▲ |
| | | | CTNNB1 | ONC | 3.6 | 2.9 |
| | | | FGFR2 | ONC | 3.6 | 1.2 ▲ |
| | | | GRIN2A | TSG | 3.6 | 0.5 ▲ |
| | | | HRAS | ONC | 3.6 | 0.7 ▲ |

Somatic drivers: 4% MMR; 38% 6+ / 44% 6+; 58% 1-5 / 54% 1-5
Oncogenes: 27% None / 18% None; 16% 3+ / 32% 3+; 56% 1-2 / 50% 1-2
TSGs: 5% None / None; 67% 3+ / 61% 3+; 27% 1-2 / 33% 1-2

**Top cancer drivers** — 50 Patients

Legend: AMPLIFICATION (red), DELETION (dark blue), MUTATION (orange), FUSION (light blue)

## Potentially Actionable Events

### # Events / Summary

| | | Skin Other % | Pan-Cancer % | Dir |
|---|---|---|---|---|
| TMB High | | 51 | 21 ▲ |
| CDKN2A | | 29 | 24 ▲ |
| PTCH1 | | 27 | 0.5 ▲ |
| PTEN | | 11 | 13 |
| EGFR | | 5.5 | 5.1 |
| ERBB2 | | 5.5 | 5.6 |
| CDK12 | | 3.6 | 0.9 ▲ |
| CTNNB1 | | 3.6 | 2.7 |
| FGFR2 | | 3.6 | 1.1 ▲ |
| HRAS | | 3.6 | 0.6 ▲ |
| KMT2D | | 3.6 | 2.9 |
| KRAS | | 3.6 | 14 ▼ |
| BRCA2 | | 1.8 | 2.4 |
| CCNE1 | | 1.8 | 0.2 ▲ |
| CDK4 | | 1.8 | 1.9 |
| FGFR2 - KIAA1217 fusion | | 1.8 | 0 ▲ |
| KIT | | 1.8 | 1.1 |
| RET | | 1.8 | 0.2 ▲ |
| SPIDR - NRG1 fusion | | 1.8 | 0 ▲ |

Actionable: 24% None / 18% None; 24% 3+ / 26% 3+; 53% 1-2 / 56% 1-2
Best treatment option: 24% None / 18% None; 9% Oth / 14% Oth; 4% Exp / 5% Exp; 13% Off / 28% Off; 51% FDA / 36% FDA

**Top potential actionable events** — 42 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### # Events / Summary

| | Type | Skin Other % | Pan-Cancer % | Dir |
|---|---|---|---|---|
| MITF | ONC | 5.5 | 0.7 ▲ |
| ATM | TSG | 1.8 | 1 |
| CHEK2 | TSG | 1.8 | 3.2 |
| MSH2 | TSG | 1.8 | 1 |
| POLD1 | TSG | 1.8 | 0.1 ▲ |
| PTCH1 | TSG | 1.8 | 0.1 ▲ |
| RET | ONC | 1.8 | 1 |
| SDHB | TSG | 1.8 | 0.1 ▲ |
| WT1 | TSG | 1.8 | 0.2 ▲ |

Germline drivers: 82% None / 84% None; 18% 1+ / 16% 1+

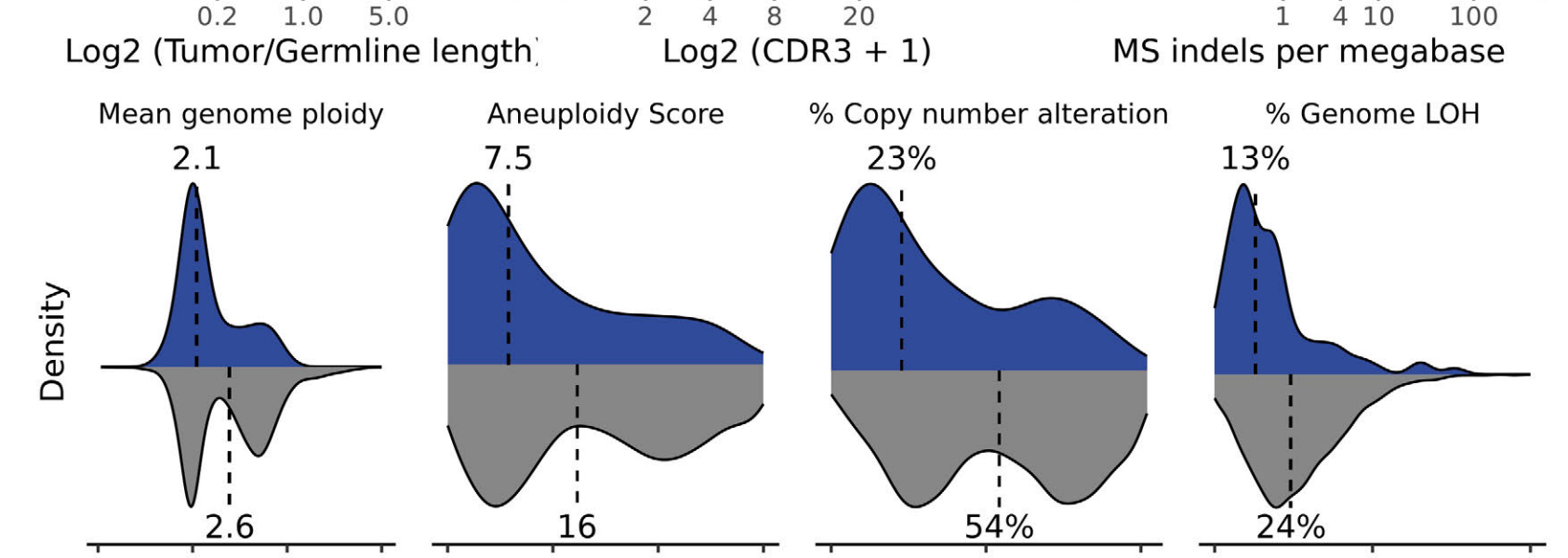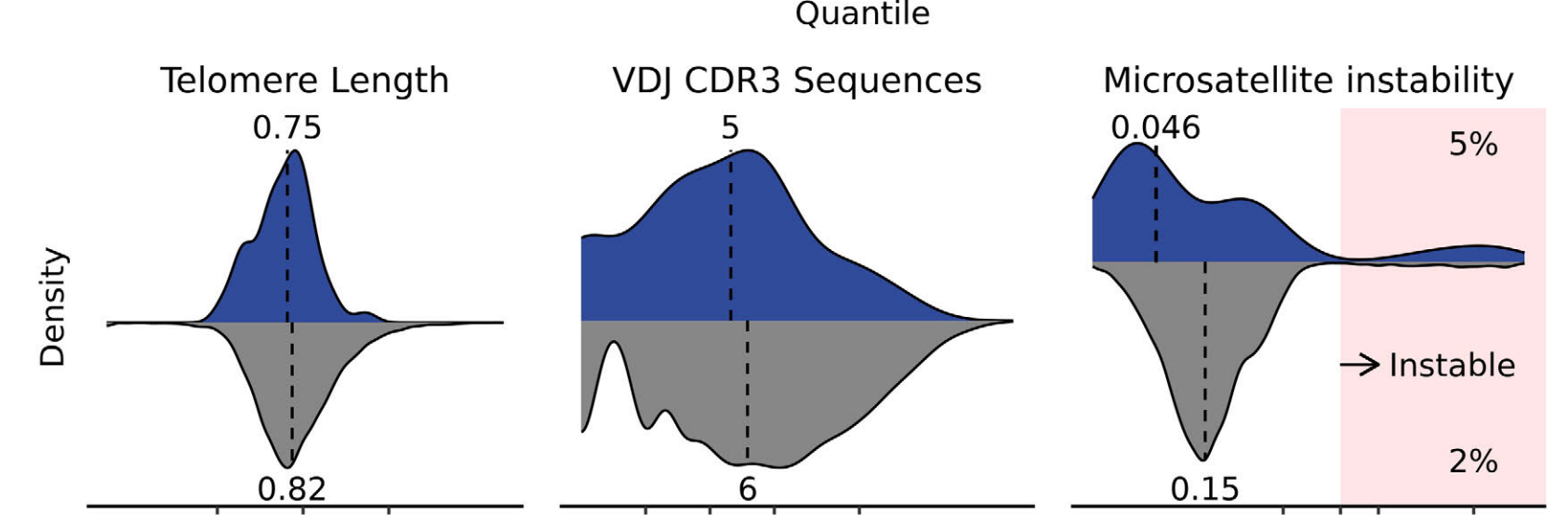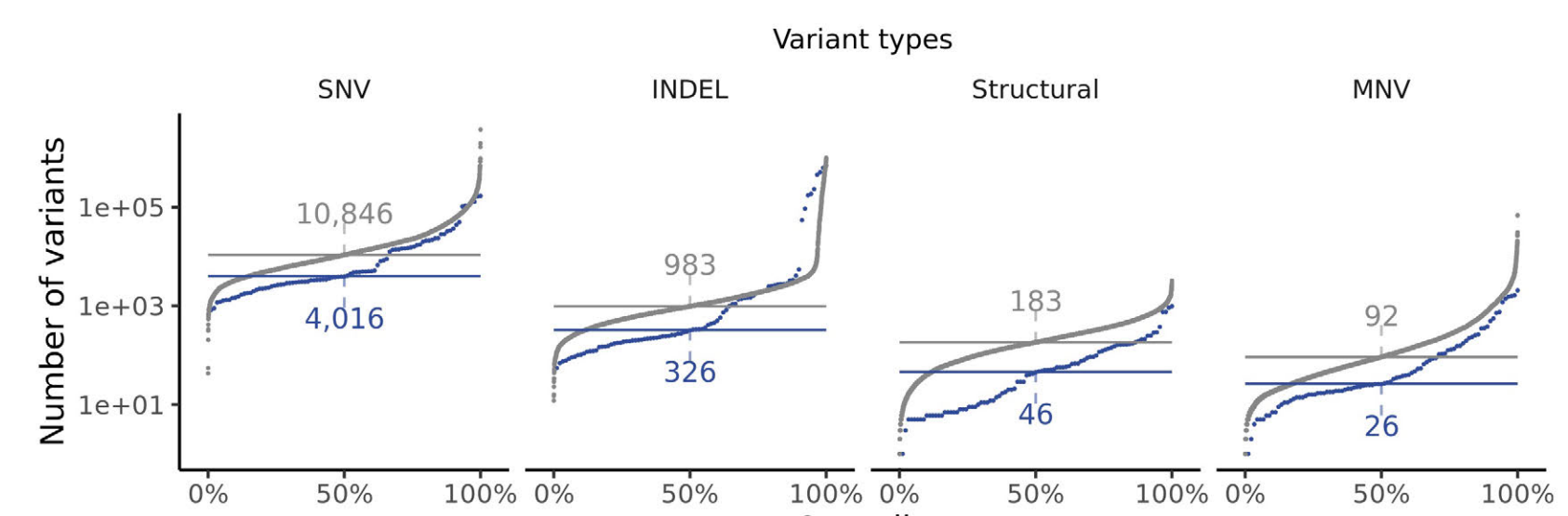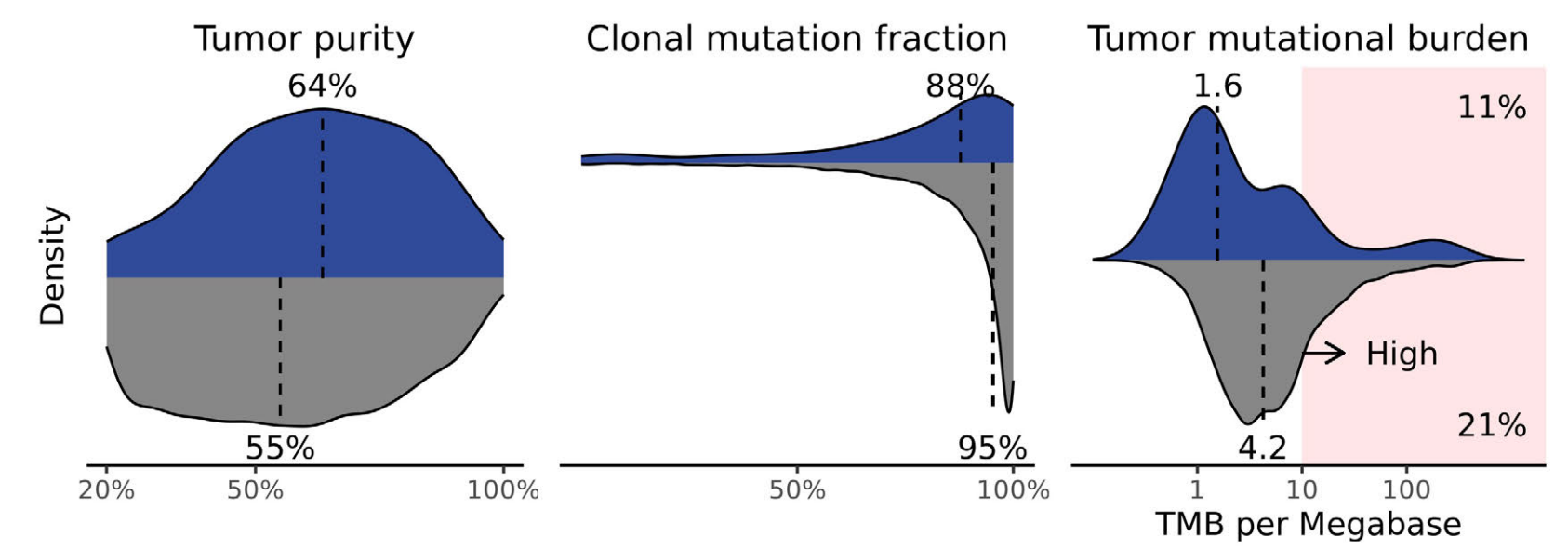**Top potential germline drivers** — 10 Patients

Legend: SMALL_VARIANT (orange)

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| | | | | | |
|---|---|---|---|---|---|
| WGS | 28 | 8 | 4 | 4 | 11 |
| Comprehensive 521 gene panel | 28 | 6 | 4 | 2 | 15 |
| Targeted 50 gene panel | 7 | 4 | 11 | 33 | |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.51 | 0.31 | 0.51 | 0.73 | 2.1 |
| Comprehensive 521 gene panel | 0.51 | 0.27 | 0.4 | 0.67 | 1.9 |
| Targeted 50 gene panel | | 0.49 | | | 0.7 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Partial CN Loss: 2

**Drug Repurposing**
- Fusion: 1
- Partial CN Loss: 1

**Experimental/Other Guidelines**
- Partial CN Loss: 2
- Fusion: 1
- Small Variant: 1
- HMZ Disruption: 1
- Partial CN Gain: 1

**Other**
- Partial CN Loss: 2
- Full CN Loss: 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- TMB High: 28

**Drug Repurposing**
- Small Variant: 5
- Fusion: 1
- Partial CN Loss: 1

**Experimental/Other Guidelines**
- Small Variant: 13
- Splice Site: 4
- Full CN Gain: 2
- Partial CN Loss: 2
- Fusion: 1

**Other**
- Small Variant: 8
- Partial CN Loss: 2
- Splice Site: 2
- Full CN Loss: 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Skin Squamous Cell Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 12 |
| RNASeq | 6 |
| Age, Sex | 7 |
| Biopsy site | 7 |
| Pretreatment | 6 |
| Treatment | 6 → |
| Response | 4 → |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | | |
|---|---|---|
| Chemo | 1 | 0 |
| Multiple | 1 | 0 |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 2 | 1 (50%) |
| Radio | 0 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

**■ Skin SKSCC   ■ Pan-Cancer**

| | Skin SKSCC | Pan-Cancer |
|---|---|---|
| TMB High | 67% | 21% |
| MSI High | 0% | 2% |
| WGD | 67% | 56% |
| Diploid Proportion | 26% | 34% |
| GIE HLA LOH | 8% | 19% |
| GIE Overall | 17% | 26% |
| Viral Insertions | 8% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
38% ... 55%

### Clonal mutation fraction
100% ... 95%

### Tumor mutational burden
53 / 67% — High
4 / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 141,152 | 1,734 | 183 | 3,559 |
| | 10,846 | 983 | 162 | 92 |

Number of variants vs Quantile

### Telomere Length
1.1 / 0.82 — Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
13 / 6 — Log2 (CDR3 + 1)

### Microsatellite instability
0.17 / 0% — Instable
0.15 / 2%
MS indels per megabase

### Mean genome ploidy
3.3 / 2.6

### Aneuploidy Score
30 / 16

### % Copy number alteration
81% / 54%

### % Genome LOH
22% / 24%

## Processes Underlying Mutations

- UV light: 81%
- Chemical exposure: 5%
- APOBEC: 4%
- DNA damage repair: 1%
- Ageing: 1%
- Tobacco: 0%
- Unknown: 7%

**Skin SKSCC** 12 Patients
**Pan-Cancer** 6790 Patients

Skin

## Copy Number Alteration Profile

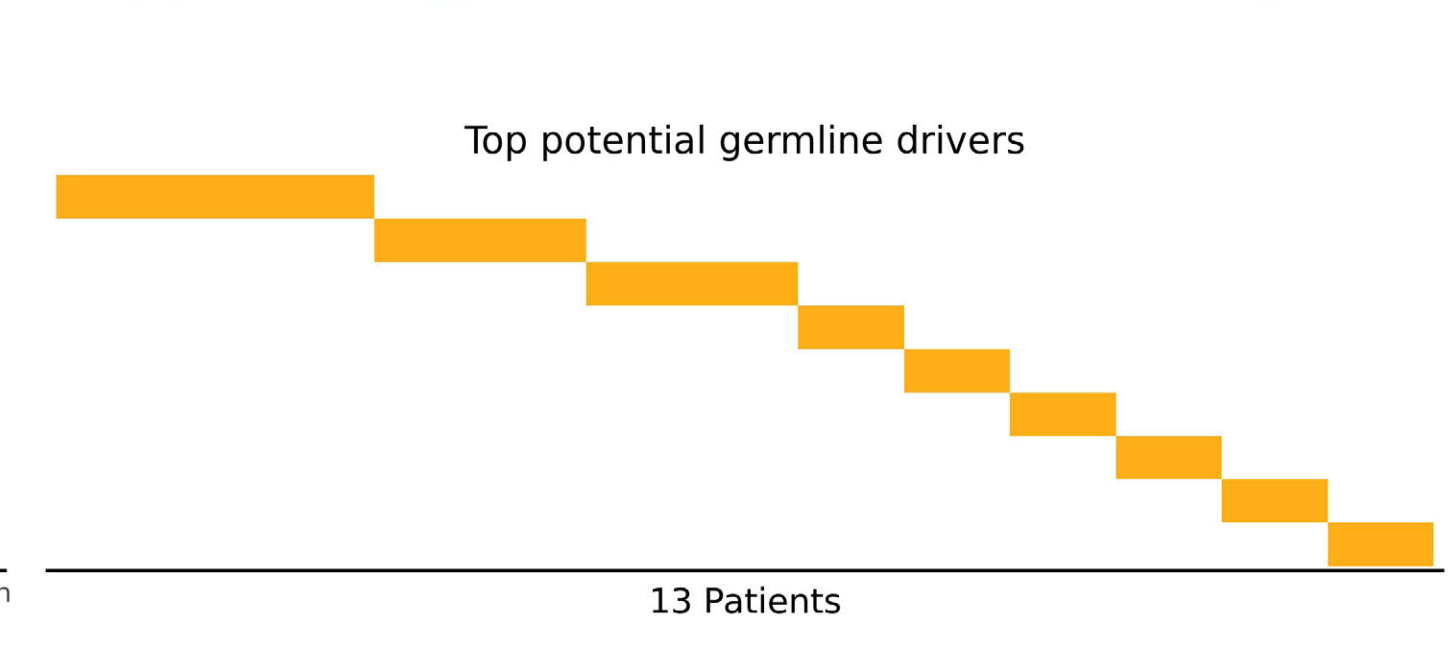(circular genome plot — chromosomes 1–22, X, Y; labelled genes: XRCC1, CALR, STK11, PARD6G, TGFBR2, KRAS, CD44, EGFR, CDKN2A)

## Cancer Driver Landscape

### # Events / Summary

| | | Type | TSG/ONC | Skin SKSCC % | Pan-Cancer % | Direction |
|---|---|---|---|---|---|---|
| Somatic drivers | | TP53 | TSG | 83 | 55 | ▲ |
| | | TERT | ONC | 75 | 13 | ▲ |
| | | CDKN2A | TSG | 58 | 25 | ▲ |
| | | NOTCH1 | TSG | 33 | 1.5 | ▲ |
| | | APC | TSG | 17 | 14 | |
| | | EGFR | ONC | 17 | 5.4 | ▲ |
| | | PARD6G | TSG | 17 | 0.3 | ▲ |
| | | STK11 | TSG | 17 | 4.1 | ▲ |
| | | TGFBR2 | TSG | 17 | 2.7 | ▲ |
| | | AJUBA | TSG | 8.3 | 0.3 | ▲ |
| Oncogenes | | CALR | ONC | 8.3 | 0.4 | ▲ |
| | | CD44 | ONC | 8.3 | 1 | ▲ |
| | | CREBBP | TSG | 8.3 | 1.9 | ▲ |
| | | EP300 | TSG | 8.3 | 1.3 | ▲ |
| | | FAT1 | TSG | 8.3 | 1.5 | ▲ |
| | | HRAS | ONC | 8.3 | 0.7 | ▲ |
| | | KDM6A | TSG | 8.3 | 3.7 | ▲ |
| | | KIT | ONC | 8.3 | 1.8 | ▲ |
| | | KRAS | ONC | 8.3 | 15 | ▼ |
| | | NF1 | TSG | 8.3 | 5 | |
| TSGs | | PPP6C | TSG | 8.3 | 0.3 | ▲ |
| | | PTEN | TSG | 8.3 | 14 | ▼ |
| | | PTPRD | TSG | 8.3 | 3 | ▲ |
| | | RB1 | TSG | 8.3 | 11 | |
| | | RBM10 | TSG | 8.3 | 1.4 | ▲ |
| | | RHOA | ONC | 8.3 | 0.5 | ▲ |
| | | SMAD2 | TSG | 8.3 | 1.2 | ▲ |
| | | SMAD4 | TSG | 8.3 | 8 | |
| | | XRCC1 | ONC | 8.3 | 5 | ▲ |

Somatic drivers: 42% 6+ ; 58% 1-5 ; 44% 6+ ; 54% 1-5
Oncogenes: 17% None ; 25% 3+ ; 58% 1-2 ; 18% None ; 32% 3+ ; 50% 1-2
TSGs: 75% 3+ ; 25% 1-2 ; None ; 61% 3+ ; 33% 1-2

**Top cancer drivers** — 12 Patients

■ AMPLIFICATION   ■ DELETION   ■ MUTATION

## Potentially Actionable Events

### # Events / Summary

| | Skin SKSCC % | Pan-Cancer % | Direction |
|---|---|---|---|
| TMB High | 67 | 21 | ▲ |
| CDKN2A | 58 | 24 | ▲ |
| EGFR | 17 | 5.1 | ▲ |
| HRAS | 8.3 | 0.6 | ▲ |
| KIT | 8.3 | 1.1 | ▲ |
| KRAS | 8.3 | 14 | ▼ |
| PTCH1 | 8.3 | 0.5 | ▲ |
| PTEN | 8.3 | 13 | ▼ |

Actionable: 17% None ; 17% 3+ ; 67% 1-2 ; 18% None ; 26% 3+ ; 56% 1-2
Best treatment option: 17% None ; 17% Oth ; Exp ; Off ; 67% FDA ; 18% None ; 14% Oth ; 5% Exp ; 28% Off ; 36% FDA

**Top potential actionable events** — 10 Patients

■ FDA Approved   ■ Drug Repurposing   ■ Experimental/Other Guidelines   ■ Other

## Germline Predisposition

### # Events / Summary

| | Type | TSG | Skin SKSCC % | Pan-Cancer % | Direction |
|---|---|---|---|---|---|
| POLD1 | TSG | | 8.3 | 0.1 | ▲ |
| PTCH1 | TSG | | 8.3 | 0.1 | ▲ |

Germline drivers: 83% None ; 17% 1+ ; 84% None ; 16% 1+

**Top potential germline drivers** — 2 Patients

■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved   ■ Drug Repurposing   ■ Experimental/Other Guidelines   ■ Other   □ None

### Highest evidence level treatment option identified by test strategy

| | FDA | Drug Rep | Exp | Other |
|---|---|---|---|---|
| WGS | 8 | 2 | 1 | 1 |
| Comprehensive 521 gene panel | 8 | 2 | 2 | |
| Targeted 50 gene panel | 1 | 2 | 6 | 3 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | Total |
|---|---|---|---|---|
| WGS | 0.67 | 0.25 | 1.2 | 2.3 |
| Comprehensive 521 gene panel | 0.67 | 0.25 | 1.2 | 2.2 |
| Targeted 50 gene panel | | | 1.1 | 1.3 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other
Partial CN Loss — 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High — 8
Drug Repurposing: Small Variant — 1
Experimental/Other Guidelines: Small Variant — 1
Other: Partial CN Loss — 1 ; Splice Site — 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Small Intestine Neuroendocrine

**Hartwig** MEDICAL FOUNDATION

Website: https://www.hartwigmedicalfoundation.nl
Tools: https://github.com/hartwigmedical/hmftools
Database: https://www.hartwigmedicalfoundation.nl/en/data/database/

## Cohort Metadata

### Data availability

Number of patients with data

- WGS: 54
- RNASeq: 41
- Age, Sex: 48
- Biopsy site: 46
- Pretreatment: 48
- Treatment: 39
- Response: 34

### Patients with treatment and response data

Post-biopsy treatment / Responders

- Chemo: 6 / 1 (17%)
- Multiple: 1 / 1 (100%)
- Targeted: 1 / 0
- Hormonal: 24 / 1 (4%)
- Immuno: 1 / 0
- Radio: 2 / 1 (50%)
- Other: 2 / 1 (50%)
- None or NA: 0 / 0

## Tumor Characteristics

Legend: SINET (dark blue), Pan-Cancer (grey)

- TMB High: 0% / 21%
- MSI High: 0% / 2%
- WGD: 19% / 56%
- Diploid Proportion: 71% / 34%
- GIE HLA LOH: 2% / 19%
- GIE Overall: 4% / 26%
- Viral Insertions: 0% / 3%
- HRD: 2% / 6%

## Mutational Landscape

### Tumor purity
68% / 55%

### Clonal mutation fraction
79% / 95%

### Tumor mutational burden
1.1 / 4.2 — High 0% / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 2,982 | 983 / 204 | 183 / 11 | 92 / 18 |

Number of variants vs Quantile

### Telomere Length
0.66 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
3 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.029 / 0.15 — Instable 0% / 2%
MS indels per megabase

### Mean genome ploidy
2 / 2.6

### Aneuploidy Score
4.5 / 16

### % Copy number alteration
16% / 54%

### % Genome LOH
9.7% / 24%

## Processes Underlying Mutations

- Ageing: 22%
- DNA damage repair: 16%
- Chemical exposure: 12%
- APOBEC: 4%
- Tobacco: 2%
- UV light: 2%
- Unknown: 42%

SINET
54 Patients

Pan-Cancer
6790 Patients

Small intestine

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## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events

Somatic drivers: None 31% / 6+ 44%; 1-5 63% / 54%; 6% none region
Oncogenes: None 74% / 3+ 32%; 1-2 22% / 50%
TSGs: None 43% / 3+ 61%; 1-2 50% / 33%

### Summary (Top cancer drivers)

| Gene | Type | SINET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CDKN1B | TSG | 17 | 1 | ▲ |
| KRAS | ONC | 7.4 | 15 | ▲ |
| CDKN2A | TSG | 5.6 | 25 | ▼ |
| MAX | TSG | 5.6 | 0.5 | ▲ |
| PSIP1 | TSG | 5.6 | 0.8 | ▲ |
| RB1 | TSG | 5.6 | 11 | ▼ |
| TP53 | TSG | 5.6 | 55 | ▼ |
| APC | TSG | 3.7 | 14 | ▼ |
| ATM | TSG | 3.7 | 2.9 | |
| CTNNB1 | ONC | 3.7 | 2.9 | |
| FAT1 | TSG | 3.7 | 1.5 | |
| MDM2 | ONC | 3.7 | 3.3 | |
| PBRM1 | TSG | 3.7 | 3.2 | |
| ATP1A1 | ONC | 1.9 | 0.1 | ▲ |
| BCL9L | ONC | 1.9 | 0.5 | ▲ |
| BCOR | TSG | 1.9 | 0.7 | |
| BRIP1 | ONC | 1.9 | 0.3 | ▲ |
| CCND2 | ONC | 1.9 | 1.1 | |
| CDK4 | ONC | 1.9 | 2 | |
| CHD7_BEND2 | ONC | 1.9 | 0 | ▲ |
| CREBBP | TSG | 1.9 | 1.9 | |
| CYLD | TSG | 1.9 | 1.9 | |
| DICER1 | TSG | 1.9 | 0.1 | ▲ |
| EGFR | ONC | 1.9 | 5.4 | |
| EIF1AX | ONC | 1.9 | 0.6 | ▲ |
| ERBB3 | ONC | 1.9 | 0.8 | |
| EWSR1_ATF1 | ONC | 1.9 | 0.1 | ▲ |
| FGFR3 | ONC | 1.9 | 1.3 | |
| FOSL2 | TSG | 1.9 | 0.2 | ▲ |

Type / Direction. SINET (%) / Pan-Cancer (%)

32 Patients

Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

## Potentially Actionable Events

### # Events

Actionable: None 70% / 3+ 26%; 1-2 28% / 56%
Best treatment option: None 70% / Oth 14% / Exp 5% / Off 28%; Off 26% / FDA 36%

### Summary (Top potential actionable events)

| Gene | SINET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| KRAS | 7.4 | 14 | ▲ |
| CDKN2A | 5.6 | 24 | ▼ |
| ATM | 3.7 | 3.5 | |
| CTNNB1 | 3.7 | 2.7 | |
| BRCA2 | 1.9 | 2.4 | |
| BRIP1 | 1.9 | 0.4 | ▲ |
| CDK12 | 1.9 | 0.9 | |
| CDK4 | 1.9 | 1.9 | |
| EGFR | 1.9 | 5.1 | |
| FGFR3 | 1.9 | 1.2 | |
| HR deficiency | 1.9 | 5.8 | ▼ |
| NRAS | 1.9 | 2.6 | |
| PALB2 | 1.9 | 0.3 | ▲ |
| RAD54L | 1.9 | 0.3 | ▲ |
| SND1 - BRAF fusion | 1.9 | 0.1 | ▲ |
| UBR5 | 1.9 | 0.3 | ▲ |

16 Patients

Legend: Drug Repurposing, Other

## Germline Predisposition

### # Events

Germline drivers: None 85% / 84%; 1+ 15% / 16%

### Summary (Top potential germline drivers)

| Gene | Type | SINET (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MSH2 | TSG | 3.7 | 1 | ▲ |
| BRCA2 | TSG | 1.9 | 1.5 | |
| CDK12 | TSG | 1.9 | 0.1 | ▲ |
| FLCN | TSG | 1.9 | 0.1 | ▲ |
| PALB2 | TSG | 1.9 | 0.4 | ▲ |
| RAD54L | TSG | 1.9 | 0.3 | ▲ |
| SDHA | TSG | 1.9 | 0.5 | ▲ |

8 Patients

Legend: SMALL_VARIANT

## WGS vs Panel Coverage

Legend: Drug Repurposing, Experimental/Other Guidelines, Other, None

### Highest evidence level treatment option identified by test strategy

- WGS: 14 / 2 / 38
- Comprehensive 521 gene panel: 13 / 39
- Targeted 50 gene panel: 4 / 3 / 47

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

- WGS: 0.28 / 0.4
- Comprehensive 521 gene panel: 0.24 / 0.4
- Targeted 50 gene panel: 0.2

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

- FDA Approved
- Drug Repurposing: Fusion 1
- HRD 1
- Experimental/Other Guidelines
- Other: Small Variant 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

- FDA Approved
- Drug Repurposing: Small Variant 8; Fusion 1; HRD 1; Splice Site 1
- Experimental/Other Guidelines: Full CN Gain 1
- Other: Small Variant 1

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy.
Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.
Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.
Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, VDJ - variable-diversity-joining, CDR - Complementarity-determining regions.
Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.
Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6x sample ploidy; blue) and near copy neutral LOH (light blue).
Outer ring shows (percentage of tumours with high level amplification (>3x sample ploidy; dark red), moderate amplification (>2x sample ploidy; red) and low level amplification (>1.4 x sample ploidy; light red).
Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).

Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.
Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event.
TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: SINET
DOIDs included: 169, 10154
Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
-Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
-Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
-Copy number: Events for panel genes with: inner ring copy number < 0.5 or max copy number > 6 assumed covered.
-Other events: Fusions, HMZ (homozygous) Distruptions, Viral inserts, HLA type assumed not captured by panels.
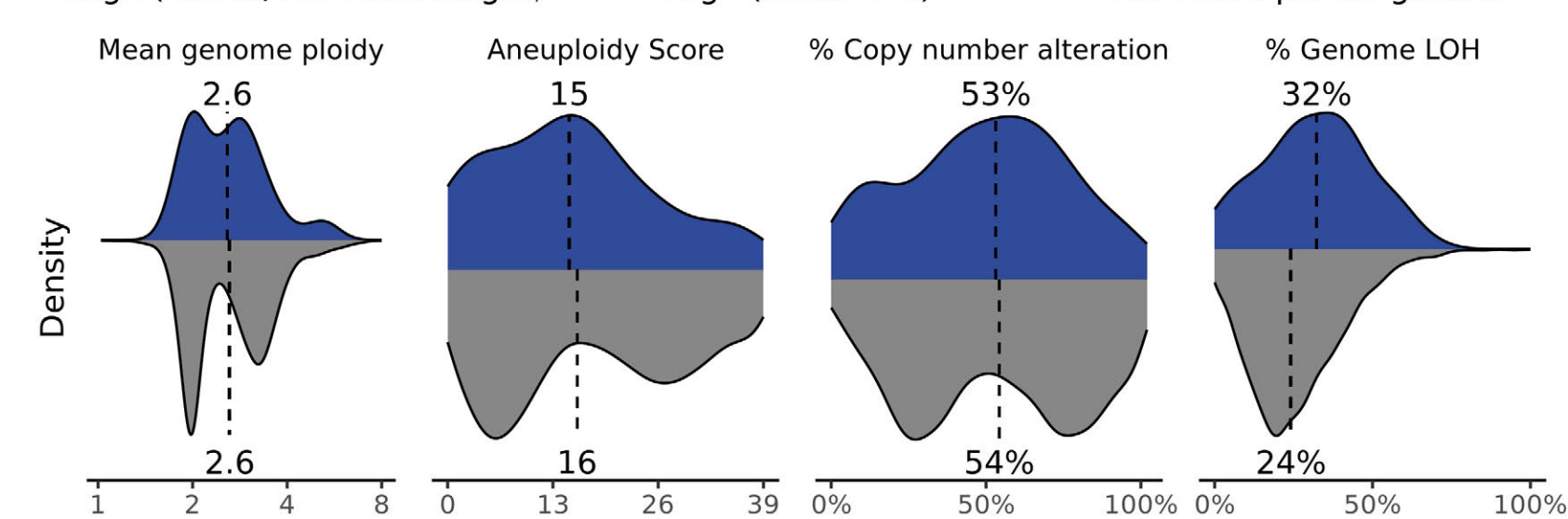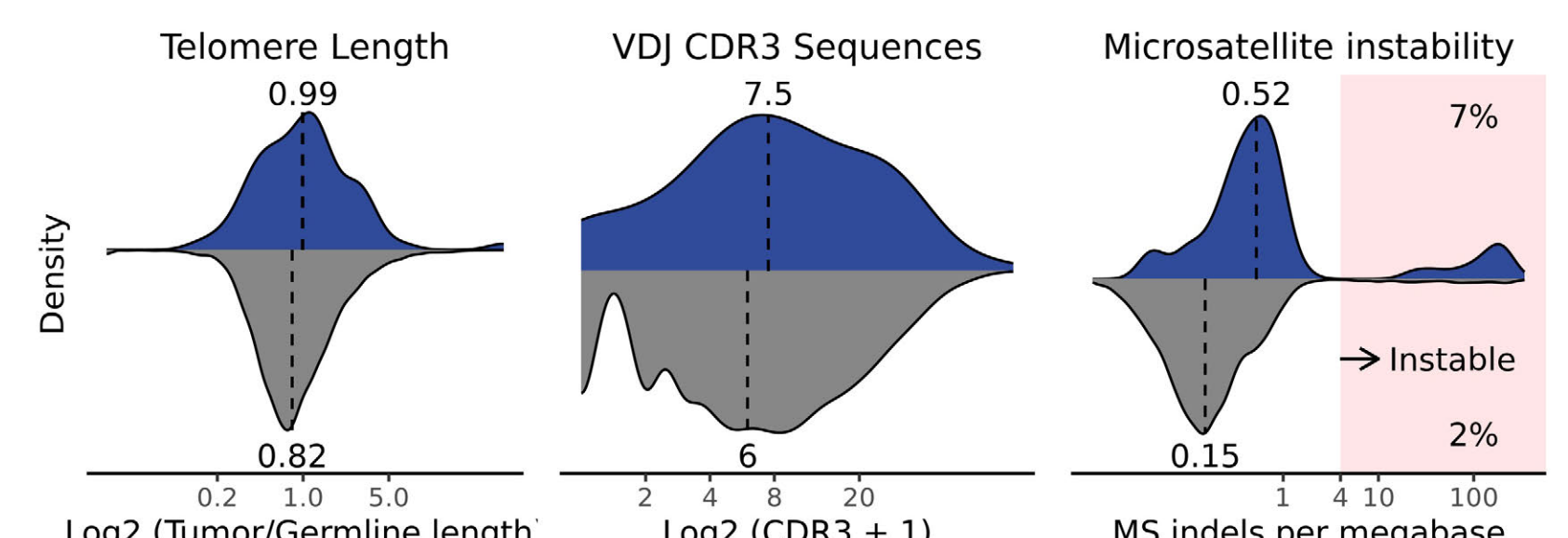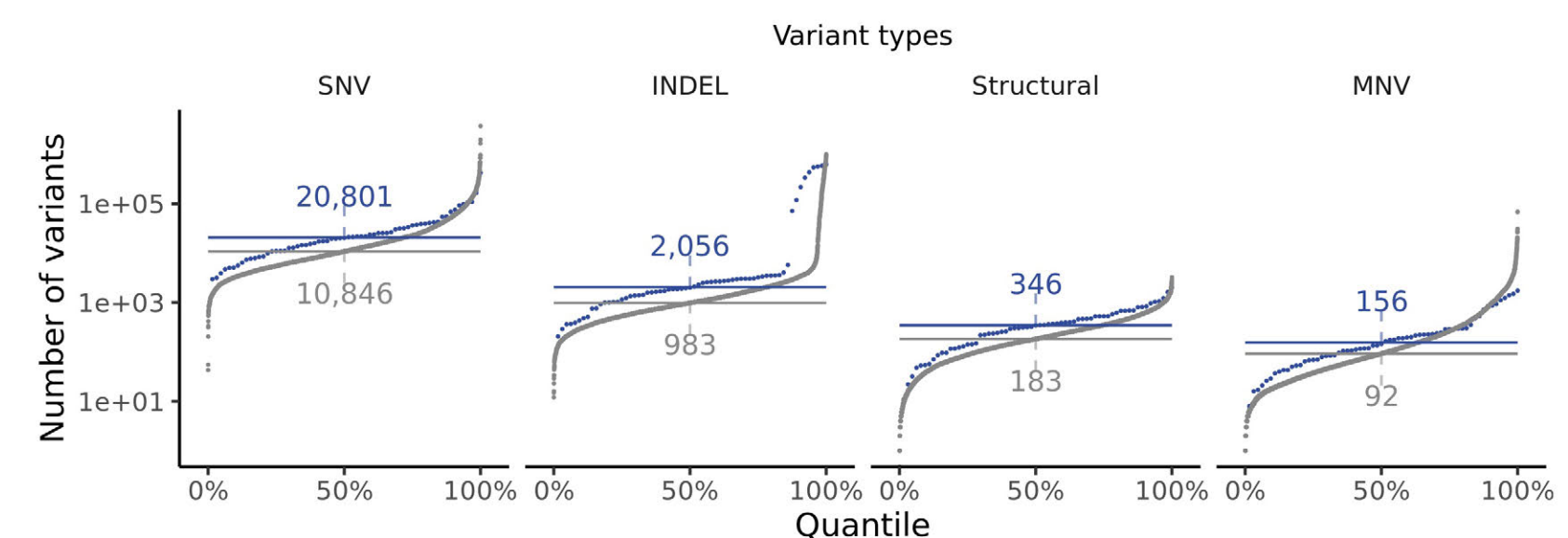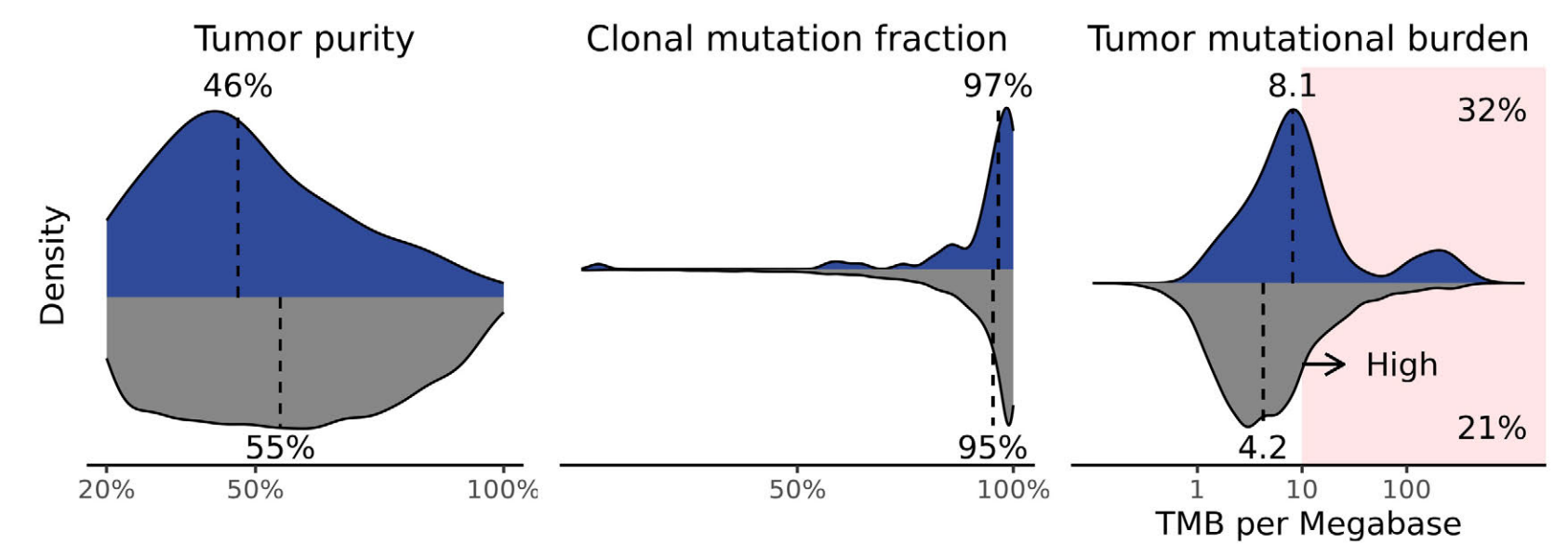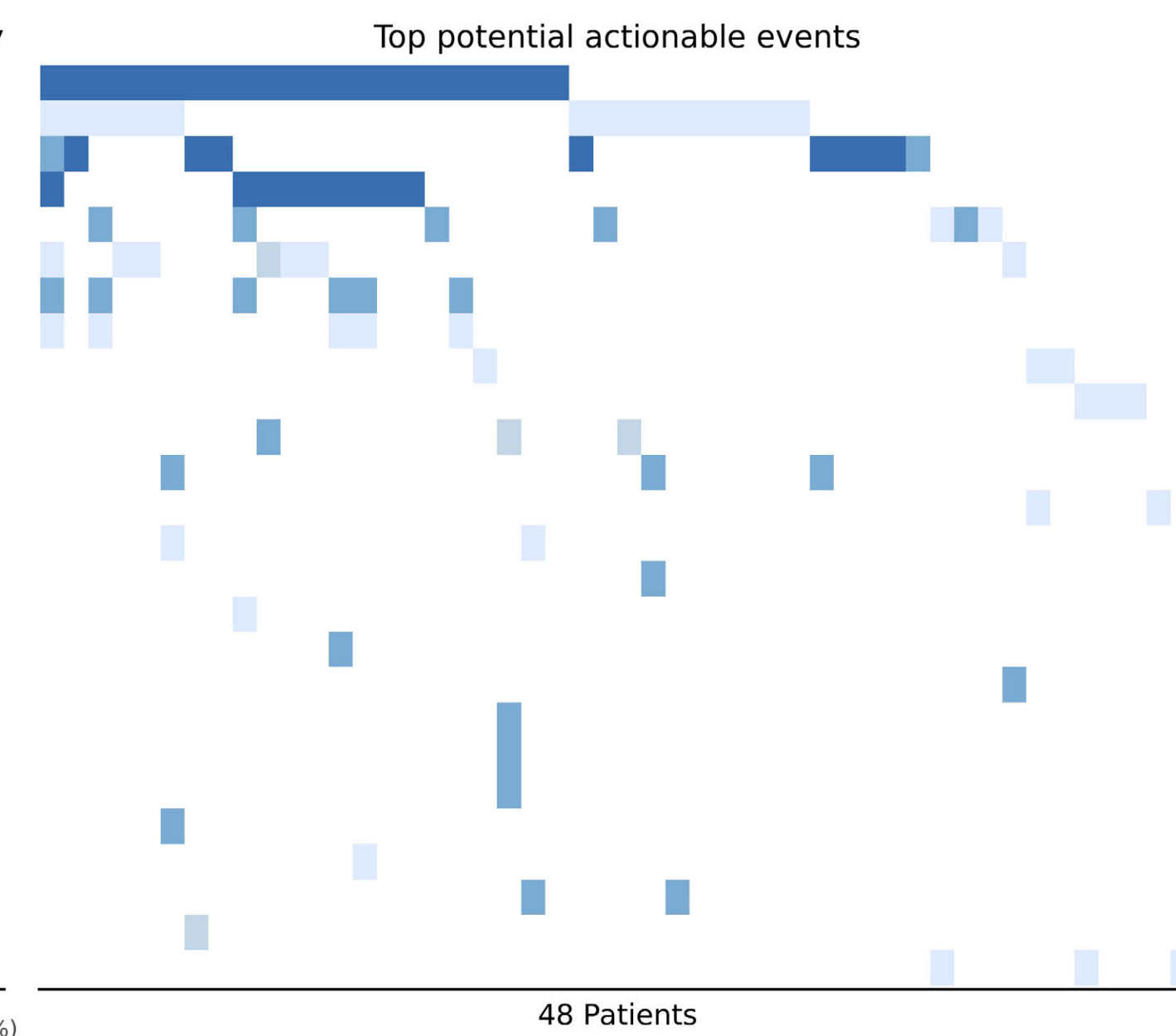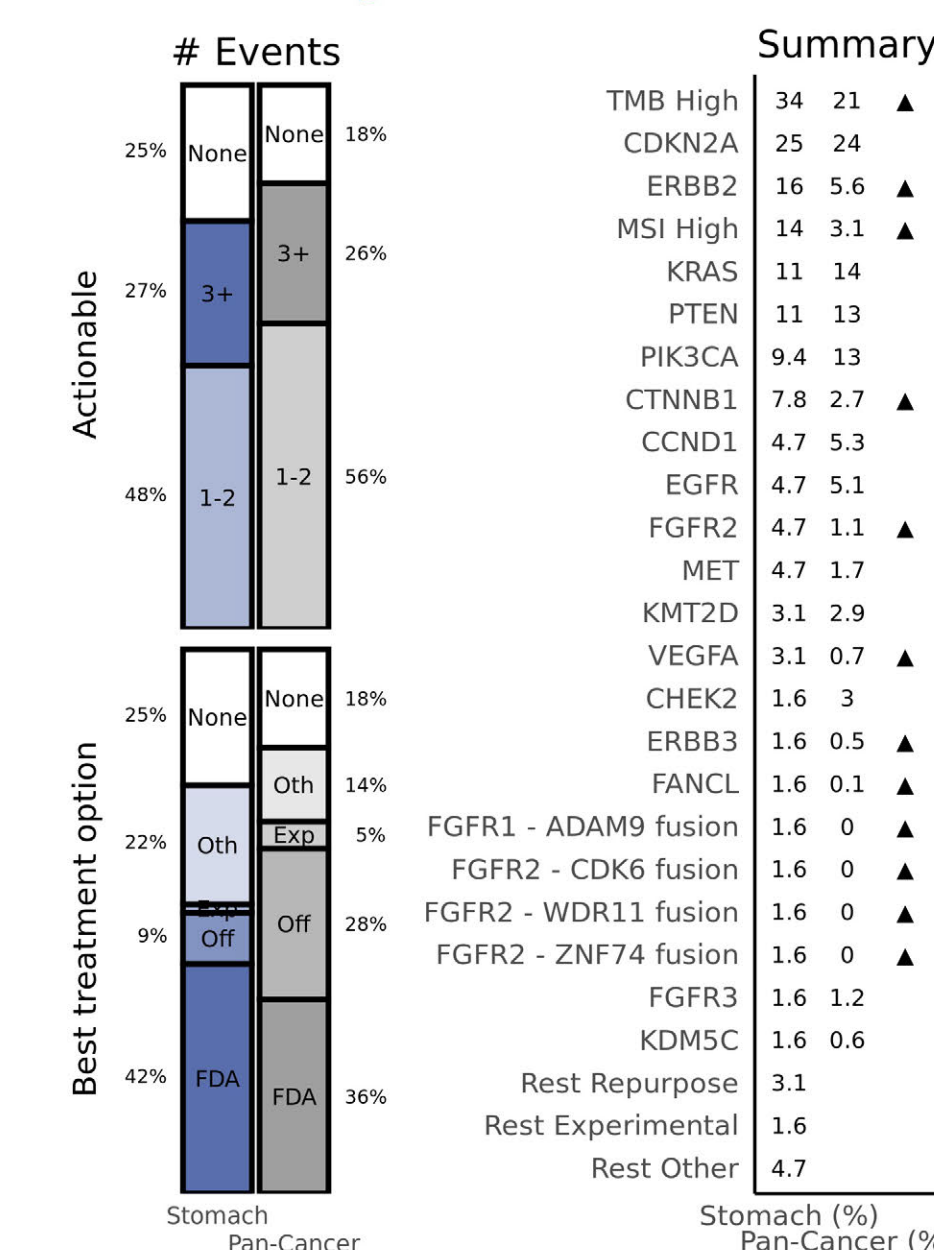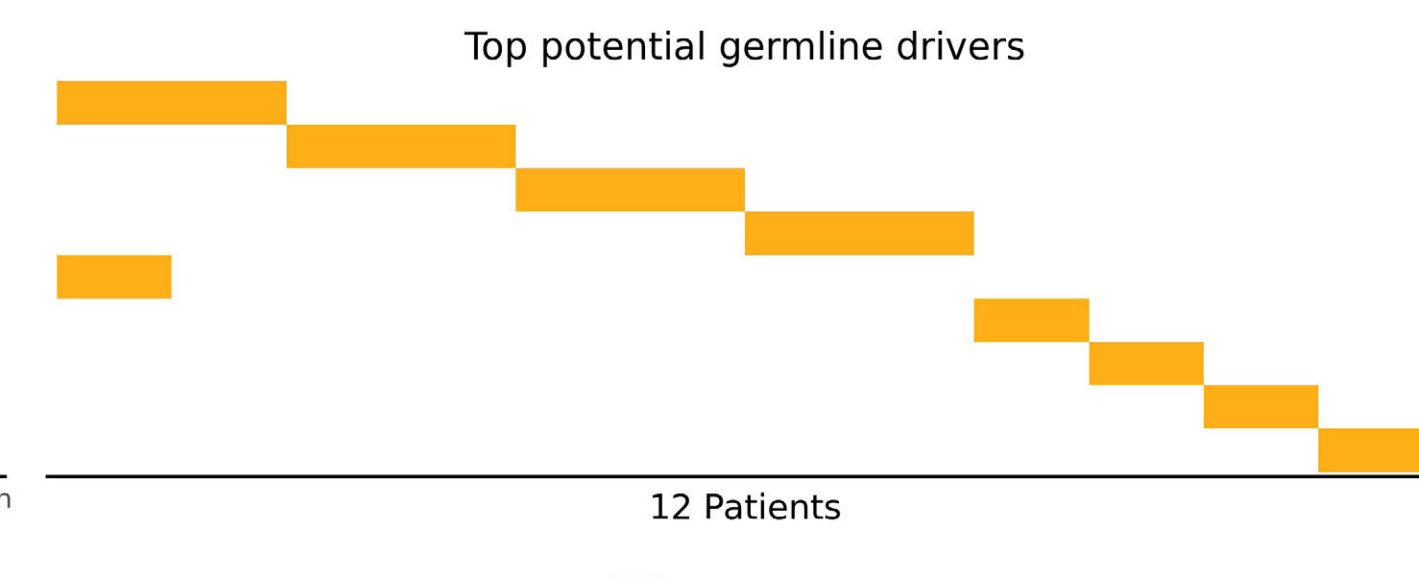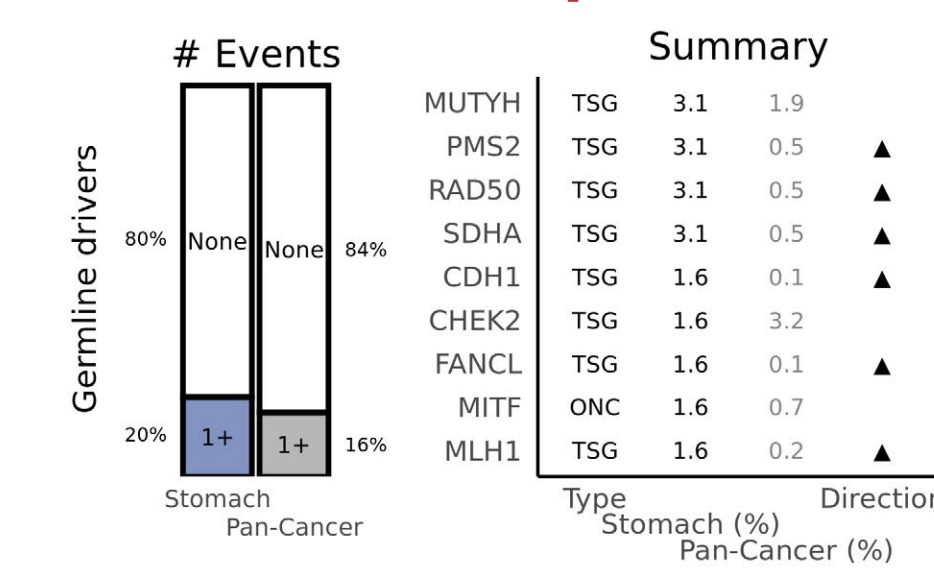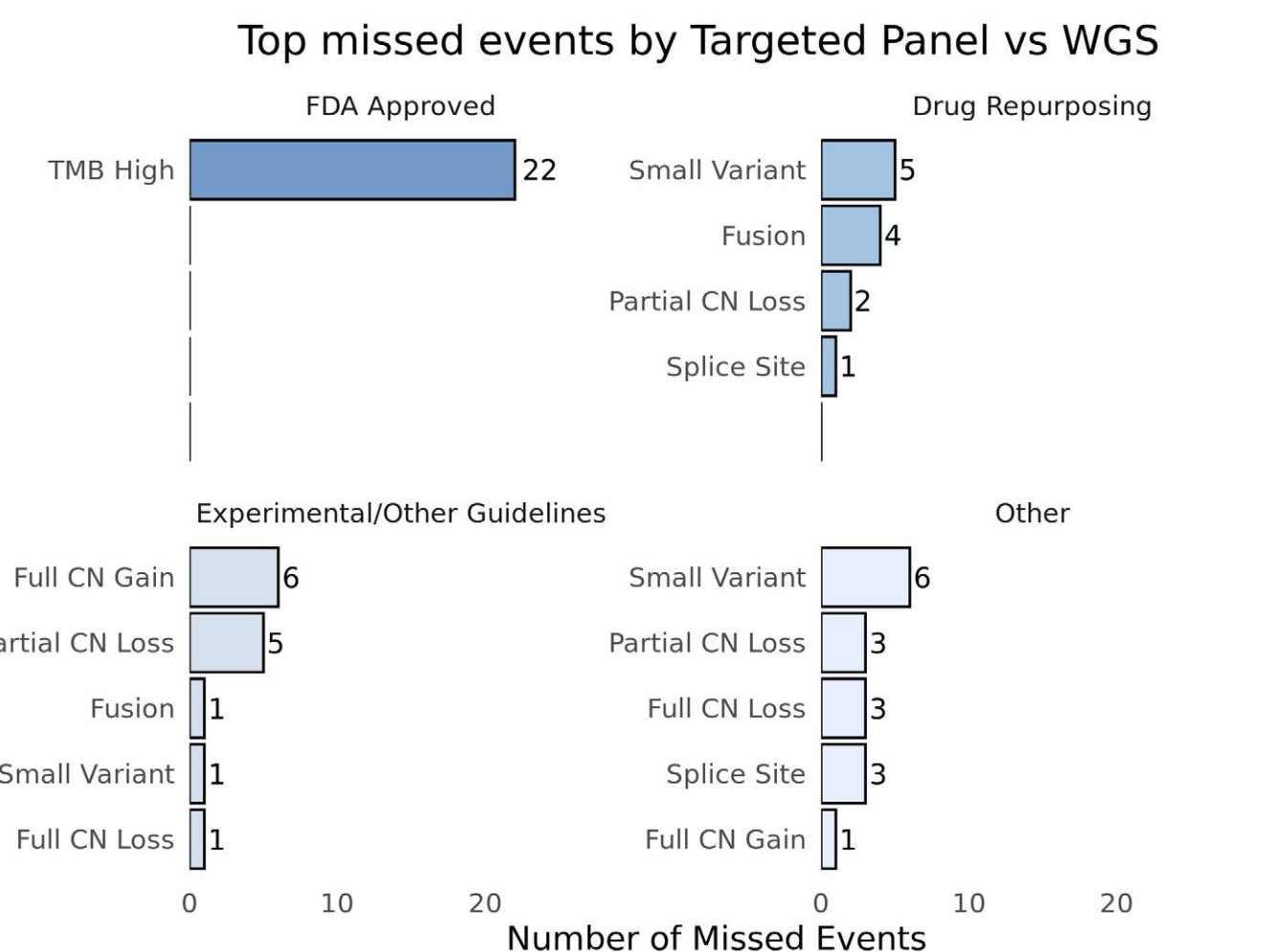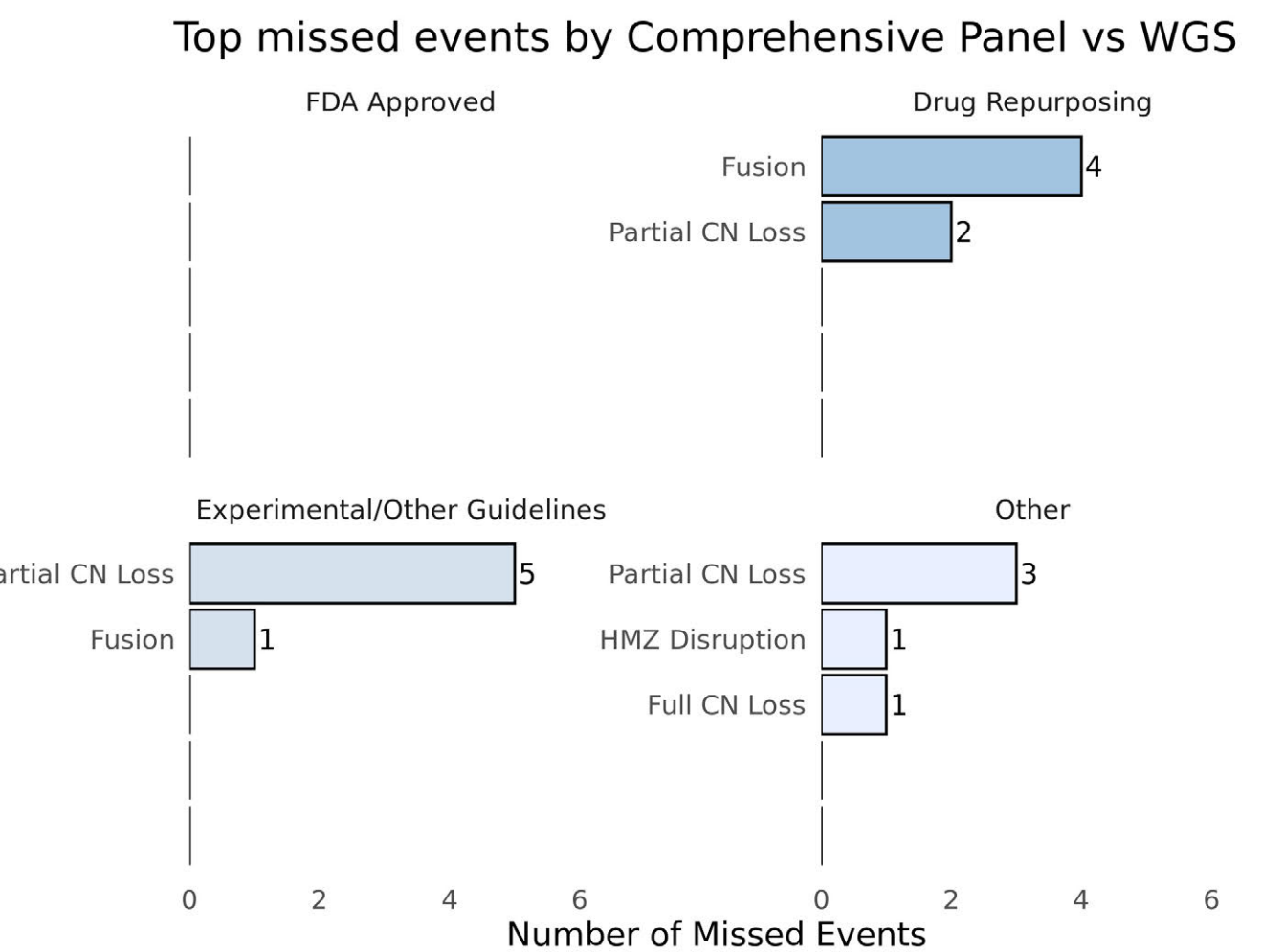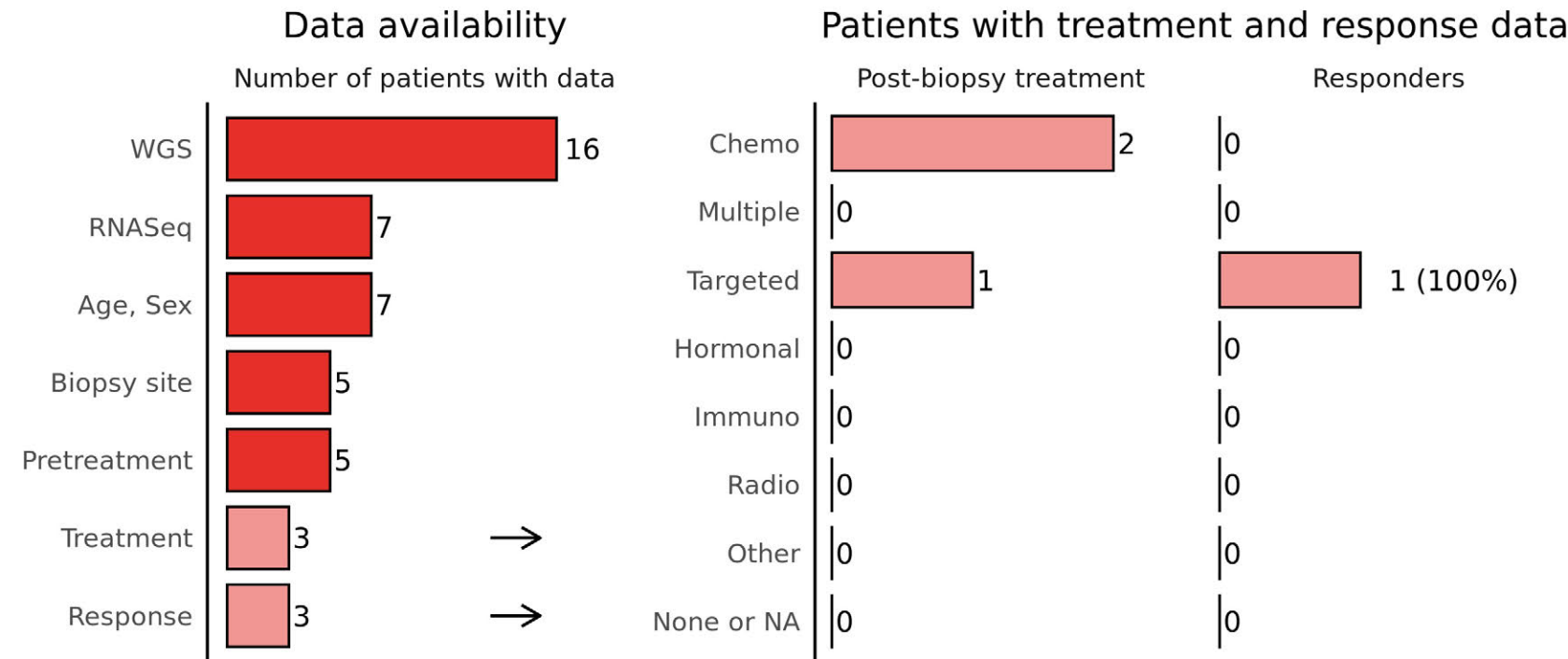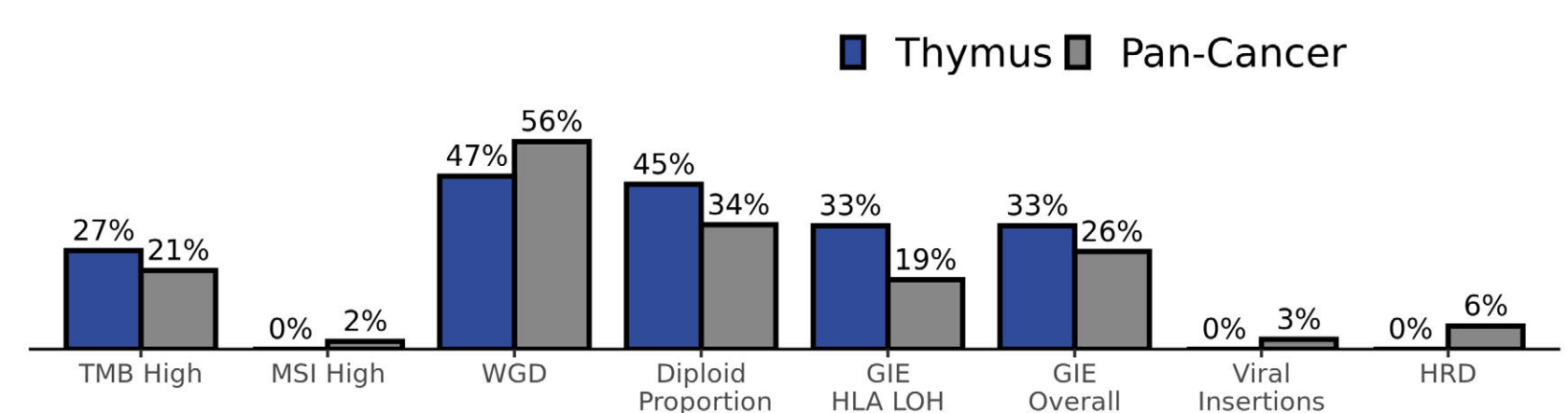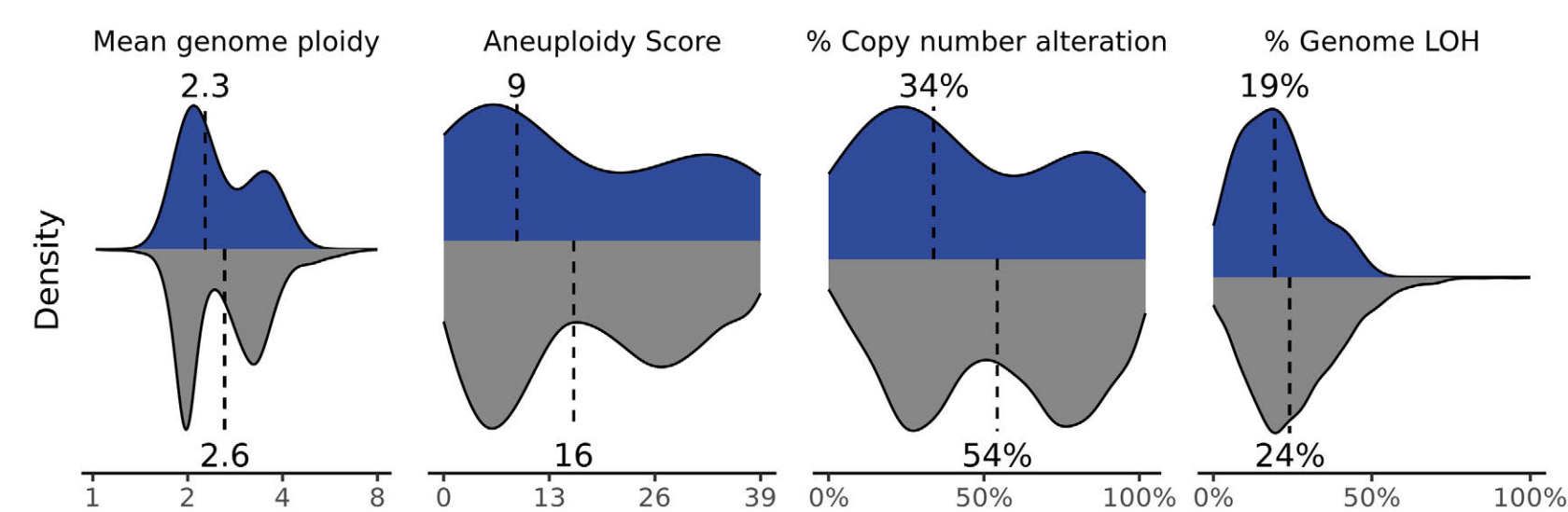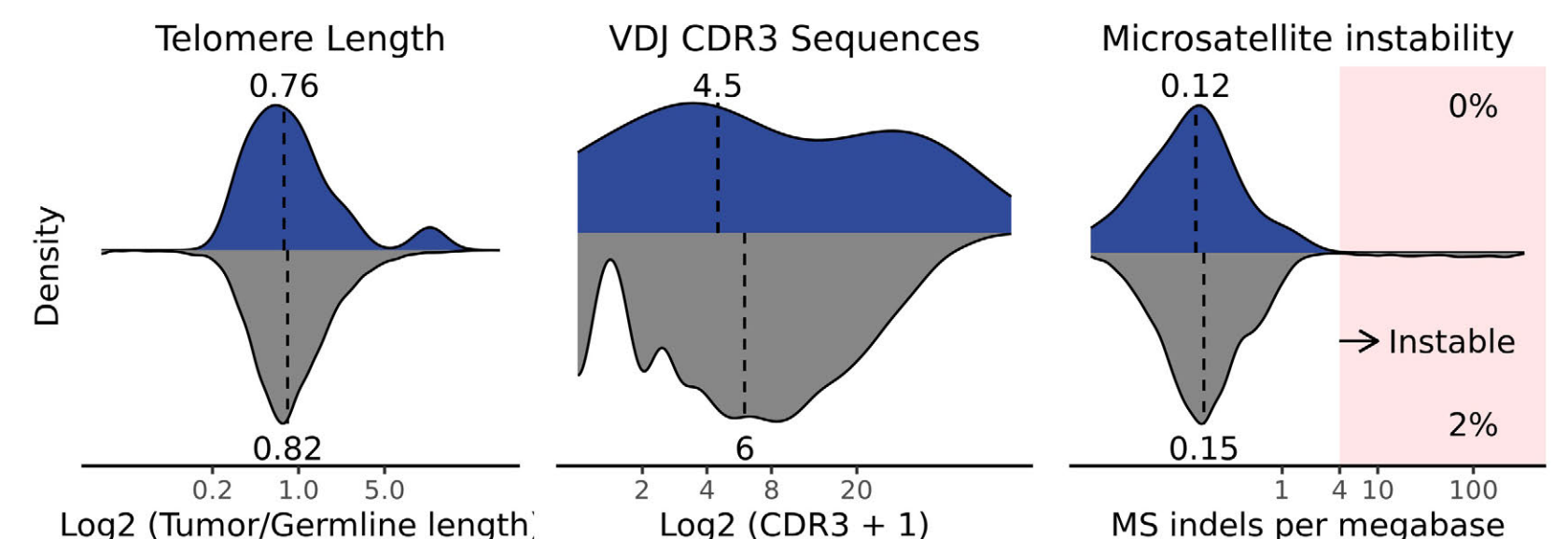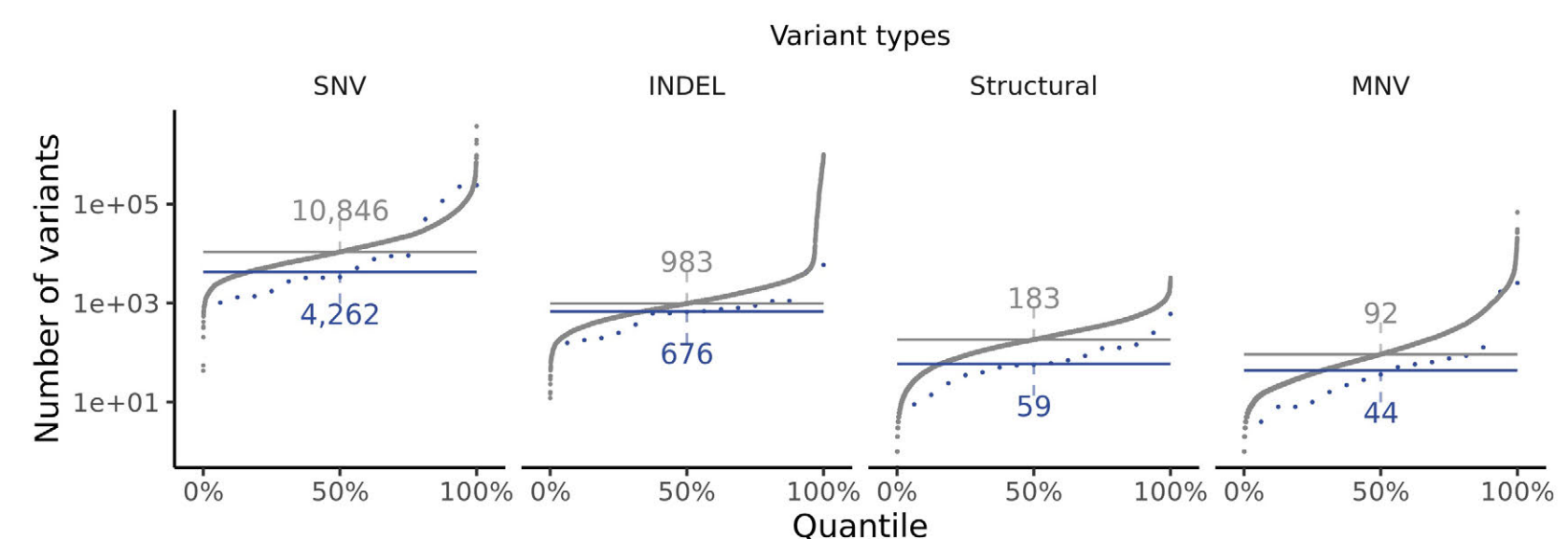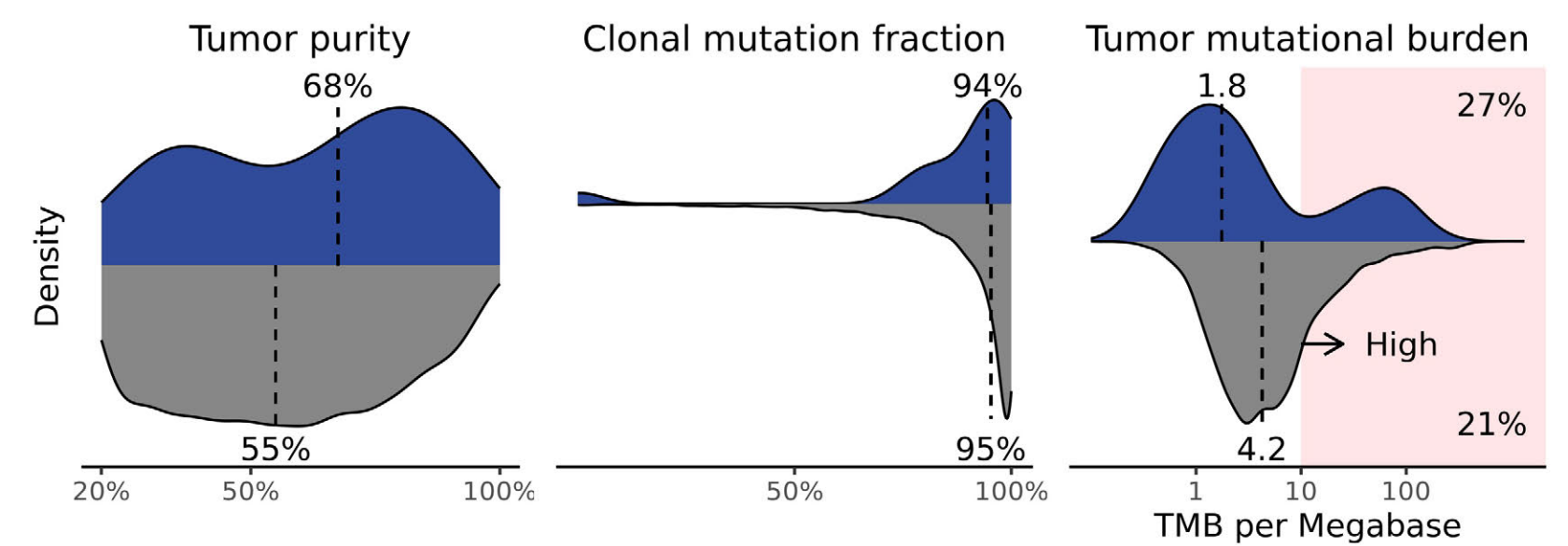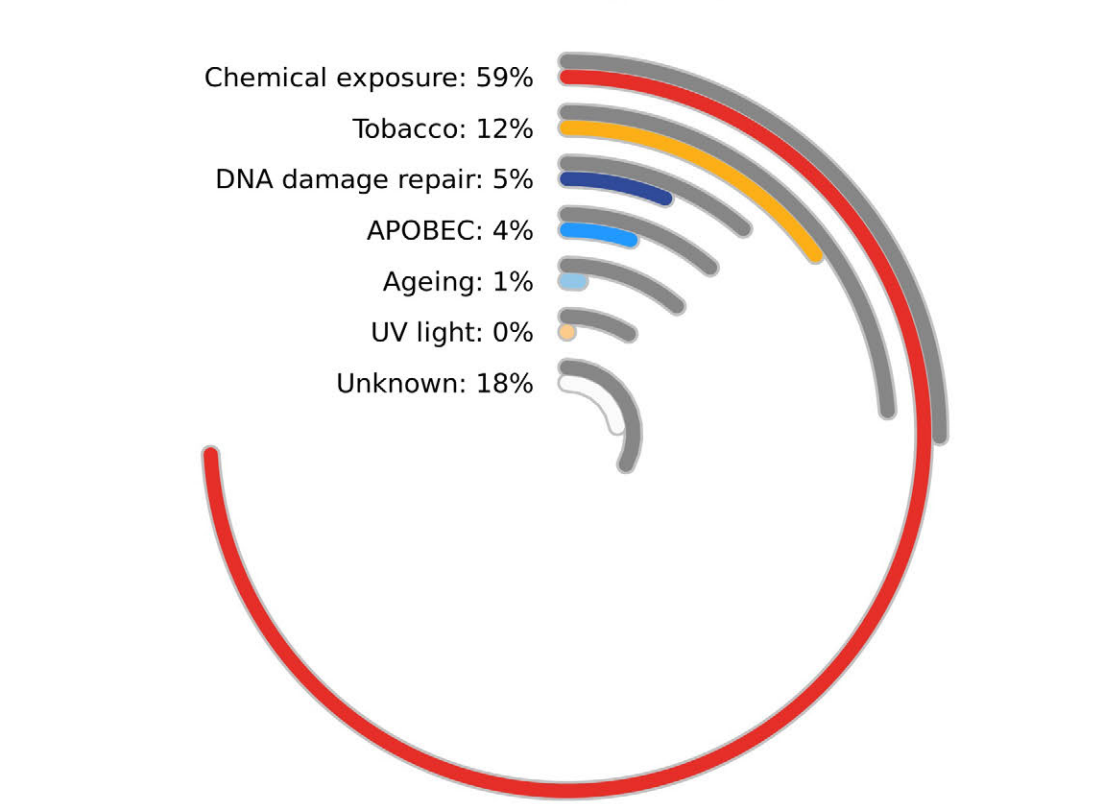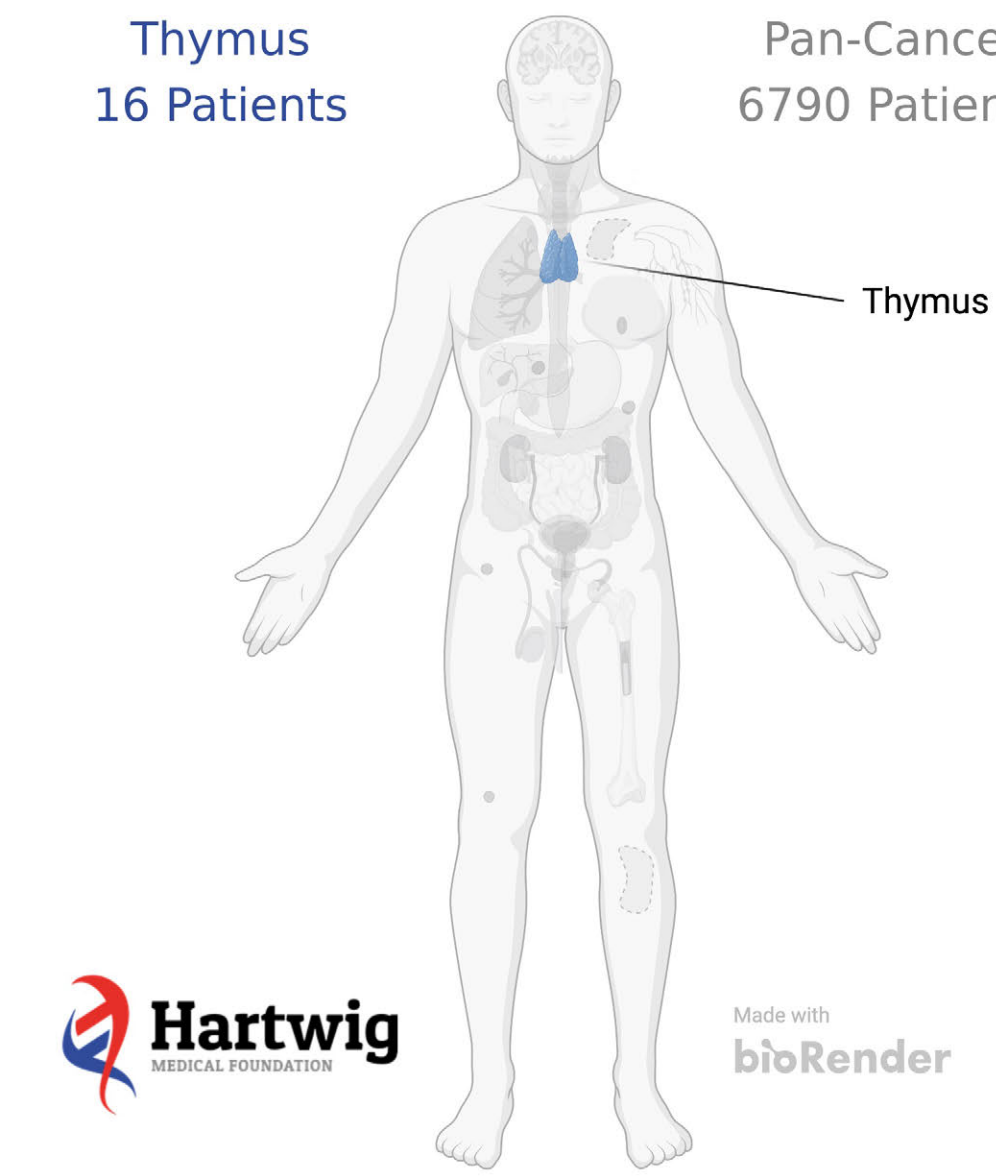** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Small Intestine Cancer

## Cohort Metadata

### Data availability

Number of patients with data

- WGS: 90
- RNASeq: 60
- Age, Sex: 70
- Biopsy site: 65
- Pretreatment: 58
- Treatment: 45 →
- Response: 38 →

### Patients with treatment and response data

Post-biopsy treatment / Responders

- Chemo: 9 / 2 (22%)
- Multiple: 1 / 1 (100%)
- Targeted: 1 / 0
- Hormonal: 24 / 1 (4%)
- Immuno: 2 / 1 (50%)
- Radio: 2 / 1 (50%)
- Other: 2 / 1 (50%)
- None or NA: 0 / 0

## Processes Underlying Mutations

- DNA damage repair: 48%
- Ageing: 16%
- Chemical exposure: 4%
- UV light: 3%
- APOBEC: 1%
- Tobacco: 1%
- Unknown: 27%

## Tumor Characteristics

Small Intestine / Pan-Cancer

- TMB High: 11% / 21%
- MSI High: 5% / 2%
- WGD: 27% / 56%
- Diploid Proportion: 61% / 34%
- GIE HLA LOH: 16% / 19%
- GIE Overall: 20% / 26%
- Viral Insertions: 0% / 3%
- HRD: 1% / 6%

## Mutational Landscape

### Tumor purity
64% / 55%

### Clonal mutation fraction
88% / 95%

### Tumor mutational burden
1.6 / 4.2 — High; 11% / 21%
TMB per Megabase

### Variant types

- SNV: 10,846 / 4,016
- INDEL: 983 / 326
- Structural: 183 / 46
- MNV: 92 / 26

Number of variants / Quantile

### Telomere Length
0.75 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
5 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.046 / 0.15 → Instable; 5% / 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
7.5 / 16

### % Copy number alteration
23% / 54%

### % Genome LOH
13% / 24%

Small Intestine 90 Patients
Pan-Cancer 6790 Patients
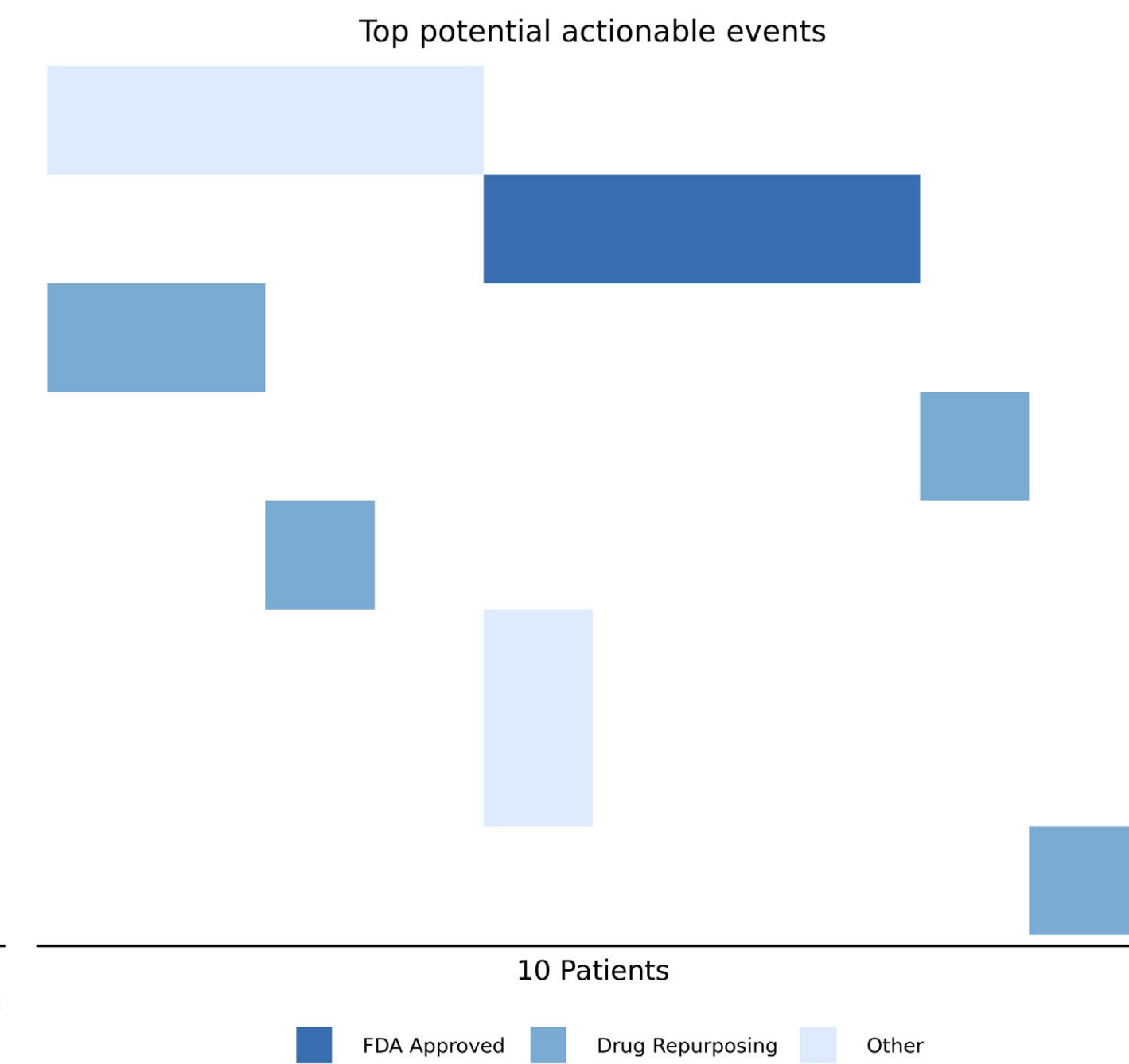Small intestine

Made with bioRender

## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers**
- None 19% / 44% 6+
- 6+ 31% / 6+
- 1-5 50% / 1-5

**Oncogenes**
- None 18% / 32% 3+
- 3+ 12% / 
- 1-2 38% / 1-2 50%

**TSGs**
- None 27% / 6%
- 3+ 38% / 3+ 61%
- 1-2 36% / 1-2 33%

| Gene | Type | Small Intestine (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| KRAS | ONC | 28 | 15 | ▲ |
| TP53 | TSG | 22 | 55 | ▼ |
| APC | TSG | 18 | 14 | |
| SMAD4 | TSG | 11 | 8 | |
| TGFBR2 | TSG | 11 | 2.7 | ▲ |
| CDKN1B | TSG | 10 | 1 | ▲ |
| CDKN2A | TSG | 10 | 25 | ▼ |
| ACVR2A | TSG | 7.8 | 2 | ▲ |
| RNF43 | TSG | 7.8 | 2.3 | ▲ |
| ATM | TSG | 6.7 | 2.9 | |
| RPL22 | TSG | 6.7 | 0.9 | ▲ |
| ERBB3 | ONC | 5.6 | 0.8 | ▲ |
| PIK3CA | ONC | 5.6 | 13 | ▼ |
| PSIP1 | TSG | 5.6 | 0.8 | ▲ |
| PTEN | TSG | 5.6 | 14 | ▼ |
| B2M | TSG | 4.4 | 1.9 | |
| ERBB2 | ONC | 4.4 | 5.7 | |
| GNAS | ONC | 4.4 | 1.5 | |
| MAP2K7 | ONC | 4.4 | 1 | ▲ |
| RB1 | TSG | 4.4 | 11 | ▼ |
| SOX9 | TSG | 4.4 | 1.8 | |
| TERT | ONC | 4.4 | 13 | ▼ |
| CTNNB1 | ONC | 3.3 | 2.9 | |
| HLA-A | TSG | 3.3 | 0.7 | ▲ |
| MAX | TSG | 3.3 | 0.5 | ▲ |
| MDM2 | TSG | 3.3 | 3.3 | |
| PRKN | TSG | 3.3 | 1.9 | |
| PTPRK_RSPO3 | ONC | 3.3 | 0.3 | ▲ |
| ZNF217 | ONC | 3.3 | 2 | |

59 Patients

AMPLIFICATION · DELETION · MUTATION · FUSION

## Potentially Actionable Events

### # Events / Summary

**Actionable**
- None 18%
- 3+ 26%
- 1-2 56%
- None 48%, 3+ 19%, 1-2 33%

**Best treatment option**
- None 18%
- Oth 14%
- Exp
- Off 28%
- FDA 36%
- None 48%, Off 31%, FDA 17%

| Event | Small Intestine (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| KRAS | 26 | 14 | ▼ |
| TMB High | 16 | 21 | ▼ |
| MSI High | 10 | 3.1 | ▲ |
| CDKN2A | 8.9 | 24 | ▼ |
| ATM | 6.7 | 3.5 | |
| ERBB2 | 4.4 | 5.6 | |
| ERBB3 | 4.4 | 0.5 | ▲ |
| PIK3CA | 4.4 | 13 | ▼ |
| PTEN | 4.4 | 13 | ▼ |
| CTNNB1 | 3.3 | 2.7 | |
| BRIP1 | 2.2 | 0.4 | ▲ |
| CDK4 | 2.2 | 1.9 | |
| HR deficiency | 2.2 | 5.8 | |
| PALB2 | 2.2 | 0.3 | ▲ |
| UBR5 | 2.2 | 0.3 | ▲ |
| AKT1 | 1.1 | 1.4 | |
| ANKS1B - NTRK3 fusion | 1.1 | 0 | ▲ |
| ARAF | 1.1 | 0.1 | ▲ |
| BRAF | 1.1 | 5.9 | ▼ |
| BRCA2 | 1.1 | 2.4 | |
| CD274 | 1.1 | 0.5 | |
| CDK12 | 1.1 | 0.9 | |
| CHEK2 | 1.1 | 3 | |
| Rest Repurpose | 7.8 | | |
| Rest Experimental | 1.1 | | |
| Rest Other | 3.3 | | |

47 Patients

FDA Approved · Drug Repurposing · Experimental/Other Guidelines · Other

## Germline Predisposition

### # Events / Summary

**Germline drivers**
- None 80% / 84%
- 1+ 20% / 1+ 16%

| Gene | Type | Small Intestine (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MSH2 | TSG | 3.3 | 1 | ▲ |
| MLH1 | TSG | 2.2 | 0.2 | ▲ |
| PALB2 | TSG | 2.2 | 0.3 | ▲ |
| APC | TSG | 1.1 | 0.2 | ▲ |
| BRCA2 | TSG | 1.1 | 1.5 | |
| CDK12 | TSG | 1.1 | 0.1 | ▲ |
| CHEK2 | TSG | 1.1 | 3.2 | |
| FLCN | TSG | 1.1 | 0.1 | ▲ |
| MSH6 | TSG | 1.1 | 0.4 | |

13 Patients

SMALL_VARIANT

## WGS vs Panel Coverage

FDA Approved · Drug Repurposing · Other · Experimental/Other Guidelines · None

### Highest evidence level treatment option identified by test strategy

# of patients in Hartwig database
- WGS: 15 / 28 / 43
- Comprehensive 521 gene panel: 14 / 28 / 3 / 44
- Targeted 50 gene panel: 9 / 21 / 4 / 55

### Average number of identified potentially actionable events identified by test strategy

Average number of actionable events per patient
- WGS: 0.27 / 0.62 / 0.32 = 1.3
- Comprehensive 521 gene panel: 0.26 / 0.58 / 0.28 = 1.2
- Targeted 50 gene panel: 0.32 = 0.6

### Top missed events by Comprehensive Panel vs WGS

FDA Approved: Fusion 1
Drug Repurposing: HRD 2, Fusion 1, Partial CN Loss 1
Experimental/Other Guidelines: Partial CN Loss 3, Full CN Gain 1
Other: Small Variant 3, Partial CN Loss 1

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 14, Fusion 1
Drug Repurposing: Small Variant 22, HRD 2, Fusion 1, Partial CN Loss 1, Splice Site 1
Experimental/Other Guidelines: Full CN Gain 4, Partial CN Loss 3, Small Variant 1, Full CN Loss 1, Partial CN Gain 1
Other: Small Variant 9, Partial CN Loss 1, Full CN Loss 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Stomach Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 64 |
| RNASeq | 38 |
| Age, Sex | 47 |
| Biopsy site | 45 |
| Pretreatment | 38 |
| Treatment | 30 → |
| Response | 22 → |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | | |
|---|---|---|
| Chemo | 8 | 1 (12%) |
| Multiple | 13 | 4 (31%) |
| Targeted | 0 | |
| Hormonal | 0 | |
| Immuno | 1 | |
| Radio | 2 | |
| Other | 0 | |
| None or NA | 0 | |

## Tumor Characteristics

Legend: ■ Stomach ■ Pan-Cancer

| | Stomach | Pan-Cancer |
|---|---|---|
| TMB High | 32% | 21% |
| MSI High | 7% | 2% |
| WGD | 68% | 56% |
| Diploid Proportion | 29% | 34% |
| GIE HLA LOH | 25% | 19% |
| GIE Overall | 34% | 26% |
| Viral Insertions | 2% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity — 46% / 55%
### Clonal mutation fraction — 97% / 95%
### Tumor mutational burden — 8.1 (32%) / 4.2 (21%) High

**TMB per Megabase**

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Stomach | 20,801 | 2,056 | 346 | 156 |
| Pan-Cancer | 10,846 | 983 | 183 | 92 |

Number of variants vs Quantile

### Telomere Length — 0.99 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences — 7.5 / 6
Log2 (CDR3 + 1)

### Microsatellite instability — 0.52 (7%) / 0.15 (2%) Instable
MS indels per megabase

### Mean genome ploidy — 2.6 / 2.6
### Aneuploidy Score — 15 / 16
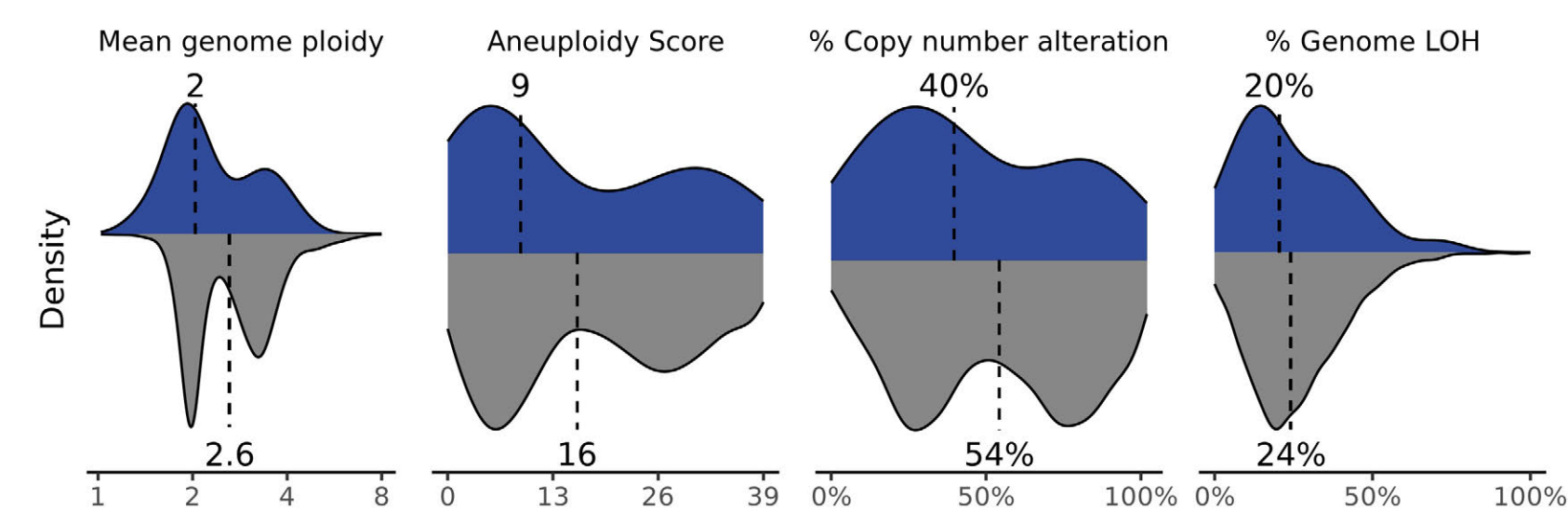### % Copy number alteration — 53% / 54%
### % Genome LOH — 32% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| DNA damage repair: | 34% |
| Ageing: | 16% |
| Chemical exposure: | 7% |
| UV light: | 3% |
| APOBEC: | 2% |
| Tobacco: | 1% |
| Unknown: | 36% |

**Stomach** 64 Patients

**Pan-Cancer** 6790 Patients

Stomach

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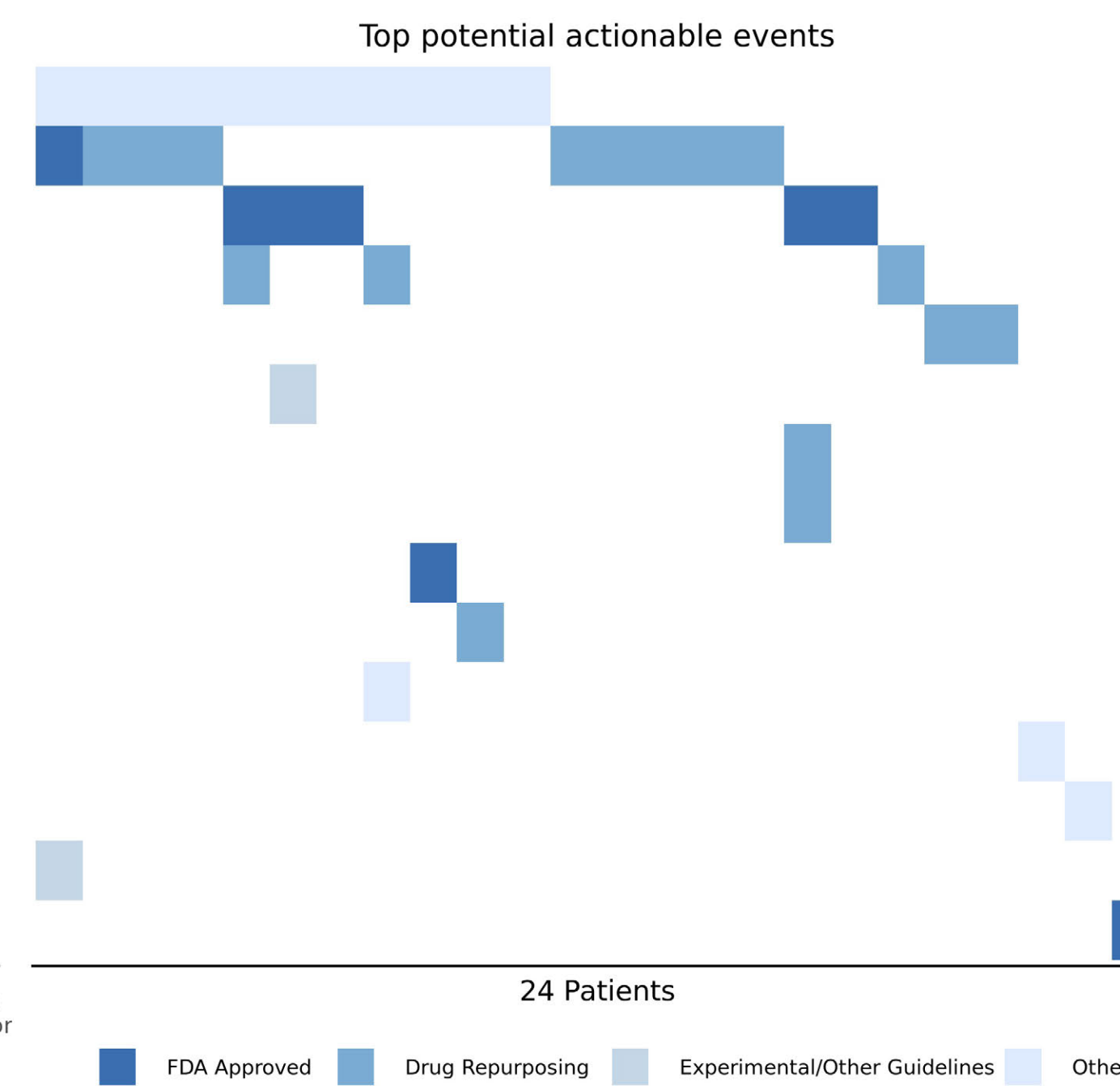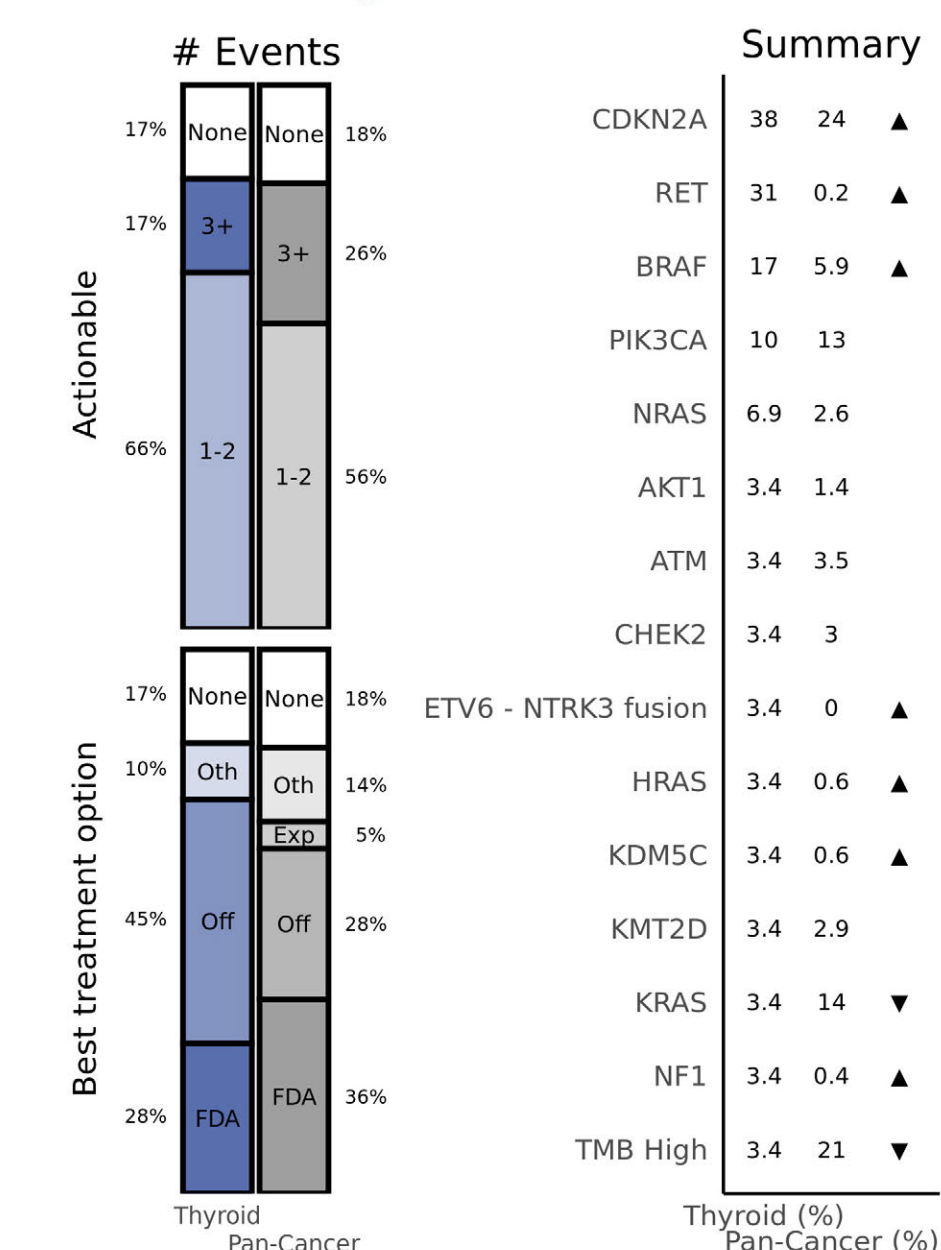
## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers** 66% / 44% (6+), 34% / 54% (1-5)

| Gene | Type | Stomach (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 73 | 55 | ▲ |
| FHIT | TSG | 34 | 4.3 | ▲ |
| CDKN2A | TSG | 28 | 25 | |
| DMD | TSG | 16 | 3.5 | ▲ |
| ERBB2 | ONC | 16 | 5.7 | ▲ |
| GMDS | TSG | 16 | 0.8 | ▲ |
| SMAD4 | TSG | 16 | 8 | |
| CCSER1 | TSG | 12 | 1.6 | ▲ |
| STS | TSG | 12 | 1.6 | ▲ |
| ARID1A | TSG | 11 | 6 | |
| KRAS | ONC | 11 | 15 | |
| MACROD2 | TSG | 11 | 1.5 | ▲ |
| PTEN | TSG | 11 | 14 | |
| PUDP | TSG | 11 | 1.4 | ▲ |
| ACVR2A | TSG | 9.4 | 2 | ▲ |
| CCNE1 | ONC | 9.4 | 2.4 | ▲ |
| PIK3CA | ONC | 9.4 | 13 | |
| SMARCA4 | TSG | 9.4 | 2.5 | ▲ |
| TGFBR2 | TSG | 9.4 | 2.7 | ▲ |
| WWOX | TSG | 9.4 | 0.4 | ▲ |
| B2M | TSG | 7.8 | 1.9 | ▲ |
| CTNNB1 | ONC | 7.8 | 2.9 | |
| PDE4D | TSG | 7.8 | 1 | ▲ |
| PRKN | TSG | 7.8 | 1.9 | ▲ |
| PTPRD | TSG | 7.8 | 3 | |
| APC | TSG | 6.2 | 14 | ▼ |
| CDH1 | TSG | 6.2 | 2.8 | |
| CDK6 | ONC | 6.2 | 0.9 | ▲ |
| CHD4 | ONC | 6.2 | 1.2 | ▲ |

**Oncogenes** 22% / 18% (None), 31% / 32% (3+), 47% / 50% (1-2)

**TSGs** 80% / 61% (3+), 20% / 33% (1-2)

### Top cancer drivers — 61 Patients

Legend: ■ AMPLIFICATION ■ DELETION ■ MUTATION
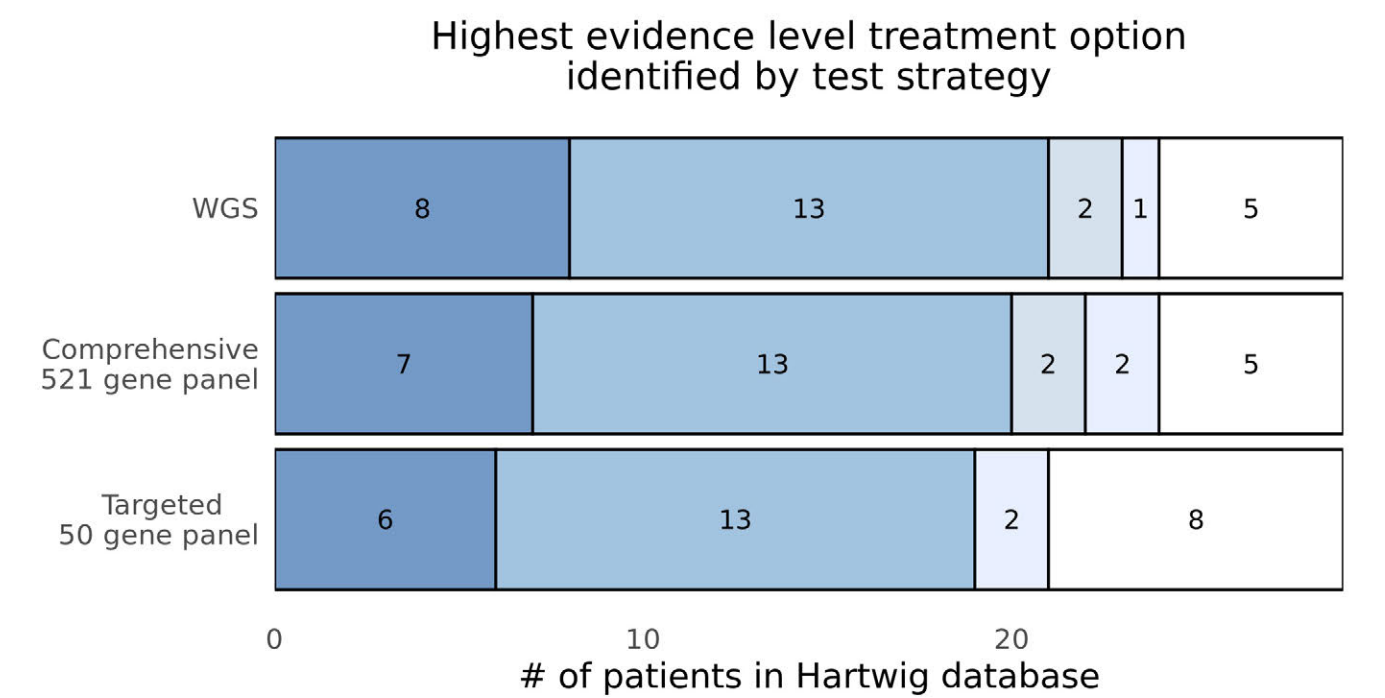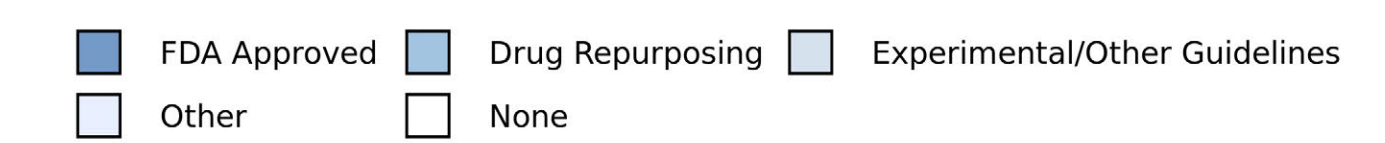
## Potentially Actionable Events

### # Events / Summary

**Actionable** 25% / 18% (None), 27% / 26% (3+), 48% / 56% (1-2)

| | | Stomach (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TMB High | | 34 | 21 | |
| CDKN2A | | 25 | 24 | |
| ERBB2 | | 16 | 5.6 | ▲ |
| MSI High | | 14 | 3.1 | ▲ |
| KRAS | | 11 | 14 | |
| PTEN | | 11 | 13 | |
| PIK3CA | | 9.4 | 13 | |
| CTNNB1 | | 7.8 | 2.7 | ▲ |
| CCND1 | | 4.7 | 5.3 | |
| EGFR | | 4.7 | 5.1 | |
| FGFR2 | | 4.7 | 1.1 | ▲ |
| MET | | 4.7 | 1.7 | ▲ |
| KMT2D | | 3.1 | 2.9 | |
| VEGFA | | 3.1 | 0.7 | ▲ |
| CHEK2 | | 1.6 | 3 | |
| ERBB3 | | 1.6 | 0.5 | ▲ |
| FANCL | | 1.6 | 0.1 | ▲ |
| FGFR1 - ADAM9 fusion | | 1.6 | 0 | ▲ |
| FGFR2 - CDK6 fusion | | 1.6 | 0 | ▲ |
| FGFR2 - WDR11 fusion | | 1.6 | 0 | ▲ |
| FGFR2 - ZNF74 fusion | | 1.6 | 0 | ▲ |
| FGFR3 | | 1.6 | 1.2 | |
| KDM5C | | 1.6 | 0.6 | |
| Rest Repurpose | | 3.1 | | |
| Rest Experimental | | 1.6 | | |
| Rest Other | | 4.7 | | |

**Best treatment option** 25% / 18% (None), 22% / 14% (Oth), 9% / 28% (Off), 42% / 36% (FDA)

### Top potential actionable events — 48 Patients

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other

## Germline Predisposition

### # Events / Summary

**Germline drivers** 80% / 84% (None), 20% / 16% (1+)

| Gene | Type | Stomach (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| MUTYH | TSG | 3.1 | 1.9 | |
| PMS2 | TSG | 3.1 | 0.5 | ▲ |
| RAD50 | TSG | 3.1 | 0.5 | ▲ |
| SDHA | TSG | 3.1 | 0.5 | ▲ |
| CDH1 | TSG | 1.6 | 0.1 | ▲ |
| CHEK2 | TSG | 1.6 | 3.2 | |
| FANCL | TSG | 1.6 | 0.1 | ▲ |
| MITF | ONC | 1.6 | 0.7 | |
| MLH1 | TSG | 1.6 | 0.2 | ▲ |

### Top potential germline drivers — 12 Patients

Legend: ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved ■ Drug Repurposing ■ Experimental/Other Guidelines ■ Other ■ None

### Highest evidence level treatment option identified by test strategy

| Test | FDA Approved | Drug Repurposing | Exp/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 27 | 7 | 10 | 8 | 12 |
| Comprehensive 521 gene panel | 27 | 5 | 9 | 7 | 16 |
| Targeted 50 gene panel | 17 | 9 | 4 | 7 | 27 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test | | | | | |
|---|---|---|---|---|---|
| WGS | 0.61 | 0.39 | 0.3 | 0.69 | 2 |
| Comprehensive 521 gene panel | 0.61 | 0.3 | 0.2 | 0.61 | 1.7 |
| Targeted 50 gene panel | 0.27 | 0.2 | 0.42 | | 1 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
| | |
|---|---|
| CDKN2A | |
| Partial CN Loss | 2 |

**Drug Repurposing**
| | |
|---|---|
| Fusion | 4 |
| Partial CN Loss | 2 |

**Experimental/Other Guidelines**
| | |
|---|---|
| Partial CN Loss | 5 |
| Fusion | 1 |

**Other**
| | |
|---|---|
| Partial CN Loss | 3 |
| HMZ Disruption | 1 |
| Full CN Loss | 1 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
| | |
|---|---|
| TMB High | 22 |

**Drug Repurposing**
| | |
|---|---|
| Small Variant | 5 |
| Fusion | 4 |
| Partial CN Loss | 2 |
| Splice Site | 1 |

**Experimental/Other Guidelines**
| | |
|---|---|
| Full CN Gain | 6 |
| Partial CN Loss | 5 |
| Fusion | 1 |
| Small Variant | 1 |
| Full CN Loss | 1 |

**Other**
| | |
|---|---|
| Small Variant | 6 |
| Partial CN Loss | 3 |
| Full CN Loss | 3 |
| Splice Site | 3 |
| Full CN Gain | 1 |

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Thymus Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 16 |
| RNASeq | 7 |
| Age, Sex | 7 |
| Biopsy site | 5 |
| Pretreatment | 5 |
| Treatment | 3 |
| Response | 3 |

**Patients with treatment and response data**

Post-biopsy treatment / Responders

| | | |
|---|---|---|
| Chemo | 2 | 0 |
| Multiple | 0 | 0 |
| Targeted | 1 | 1 (100%) |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 0 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: ■ Thymus ■ Pan-Cancer

| | TMB High | MSI High | WGD | Diploid Proportion | GIE HLA LOH | GIE Overall | Viral Insertions | HRD |
|---|---|---|---|---|---|---|---|---|
| Thymus | 27% | 0% | 47% | 45% | 33% | 33% | 0% | 0% |
| Pan-Cancer | 21% | 2% | 56% | 34% | 19% | 26% | 3% | 6% |

## Mutational Landscape

**Tumor purity** 68% / 55%

**Clonal mutation fraction** 94% / 95%

**Tumor mutational burden** 1.8 / 4.2; High 27% / 21%
TMB per Megabase

**Variant types**

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Pan-Cancer | 10,846 | 983 | 183 | 92 |
| Thymus | 4,262 | 676 | 59 | 44 |

Number of variants vs Quantile

**Telomere Length** 0.76 / 0.82
Log2 (Tumor/Germline length)

**VDJ CDR3 Sequences** 4.5 / 6
Log2 (CDR3 + 1)

**Microsatellite instability** 0.12 / 0.15; Instable 0% / 2%
MS indels per megabase

**Mean genome ploidy** 2.3 / 2.6

**Aneuploidy Score** 9 / 16

**% Copy number alteration** 34% / 54%

**% Genome LOH** 19% / 24%

## Processes Underlying Mutations

- Chemical exposure: 59%
- Tobacco: 12%
- DNA damage repair: 5%
- APOBEC: 4%
- Ageing: 1%
- UV light: 0%
- Unknown: 18%

Thymus 16 Patients
Pan-Cancer 6790 Patients

Thymus

Made with bioRender

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary

**Somatic drivers**

| | Thymus | Pan-Cancer |
|---|---|---|
| None | 12% | 12% |
| 6+ | 6+ | 44% |
| 1-5 | 75% | 1-5 54% |

**Oncogenes**

| | Thymus | Pan-Cancer |
|---|---|---|
| None | 50% | 18% |
| 3+ | 6% | 3+ 32% |
| 1-2 | 44% | 1-2 50% |

**TSGs**

| | Thymus | Pan-Cancer |
|---|---|---|
| None | 19% | 6% |
| 3+ | 25% | 3+ 61% |
| 1-2 | 56% | 1-2 33% |

| Gene | Type | Thymus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CDKN2A | TSG | 25 | 25 | |
| ATRX | TSG | 12 | 2.4 | ▲ |
| BAP1 | TSG | 12 | 2.7 | ▲ |
| GTF2I | ONC | 12 | 0.3 | ▲ |
| KIT | ONC | 12 | 1.8 | ▲ |
| NRG1 | TSG | 12 | 0.2 | ▲ |
| PPM1D | TSG | 12 | 1.7 | ▲ |
| SMARCA4 | TSG | 12 | 2.5 | ▲ |
| TP53 | TSG | 12 | 5.5 | ▼ |
| ARID2 | TSG | 6.2 | 1.8 | ▲ |
| BCOR | TSG | 6.2 | 0.7 | ▲ |
| BRD7 | TSG | 6.2 | 0.3 | ▲ |
| CHEK2 | TSG | 6.2 | 0.4 | ▲ |
| DMD | TSG | 6.2 | 3.5 | |
| ERBB3 | ONC | 6.2 | 0.8 | ▲ |
| FGFR2 | ONC | 6.2 | 1.2 | ▲ |
| FOSL2 | TSG | 6.2 | 0.2 | ▲ |
| FOXA1 | ONC | 6.2 | 2.3 | |
| GMDS | ONC | 6.2 | 0.8 | ▲ |
| HRAS | ONC | 6.2 | 0.7 | ▲ |
| KDM6A | TSG | 6.2 | 3.7 | |
| KMT2B | TSG | 6.2 | 1 | ▲ |
| MECOM | ONC | 6.2 | 0.3 | ▲ |
| MED12 | TSG | 6.2 | 1 | ▲ |
| MGA | TSG | 6.2 | 1.5 | ▲ |
| PTPN13 | TSG | 6.2 | 0.6 | ▲ |
| PUDP | TSG | 6.2 | 1.4 | ▲ |
| SOX9 | TSG | 6.2 | 1.8 | ▲ |

Top cancer drivers — 14 Patients

Legend: ■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events / Summary

**Actionable**

| | Thymus | Pan-Cancer |
|---|---|---|
| None | 38% | 18% |
| 3+ | 6% | 3+ 26% |
| 1-2 | 56% | 1-2 56% |

**Best treatment option**

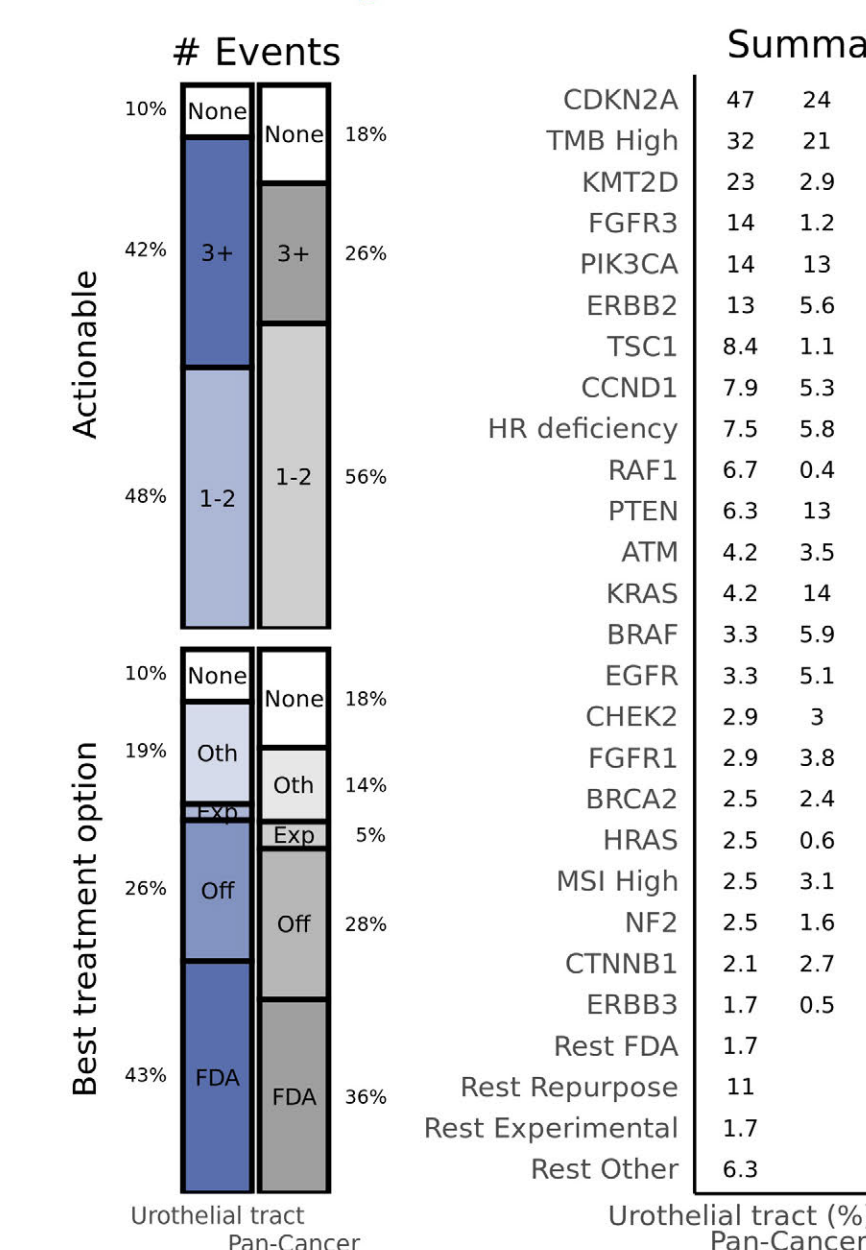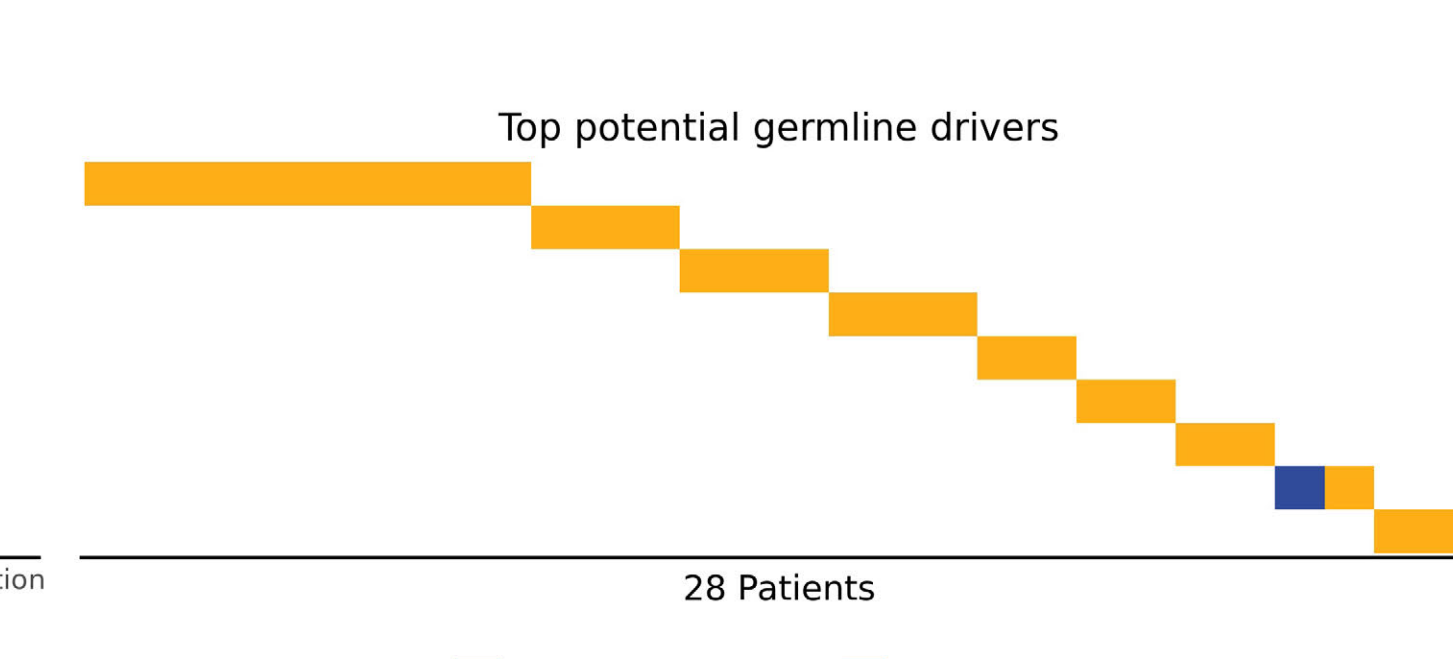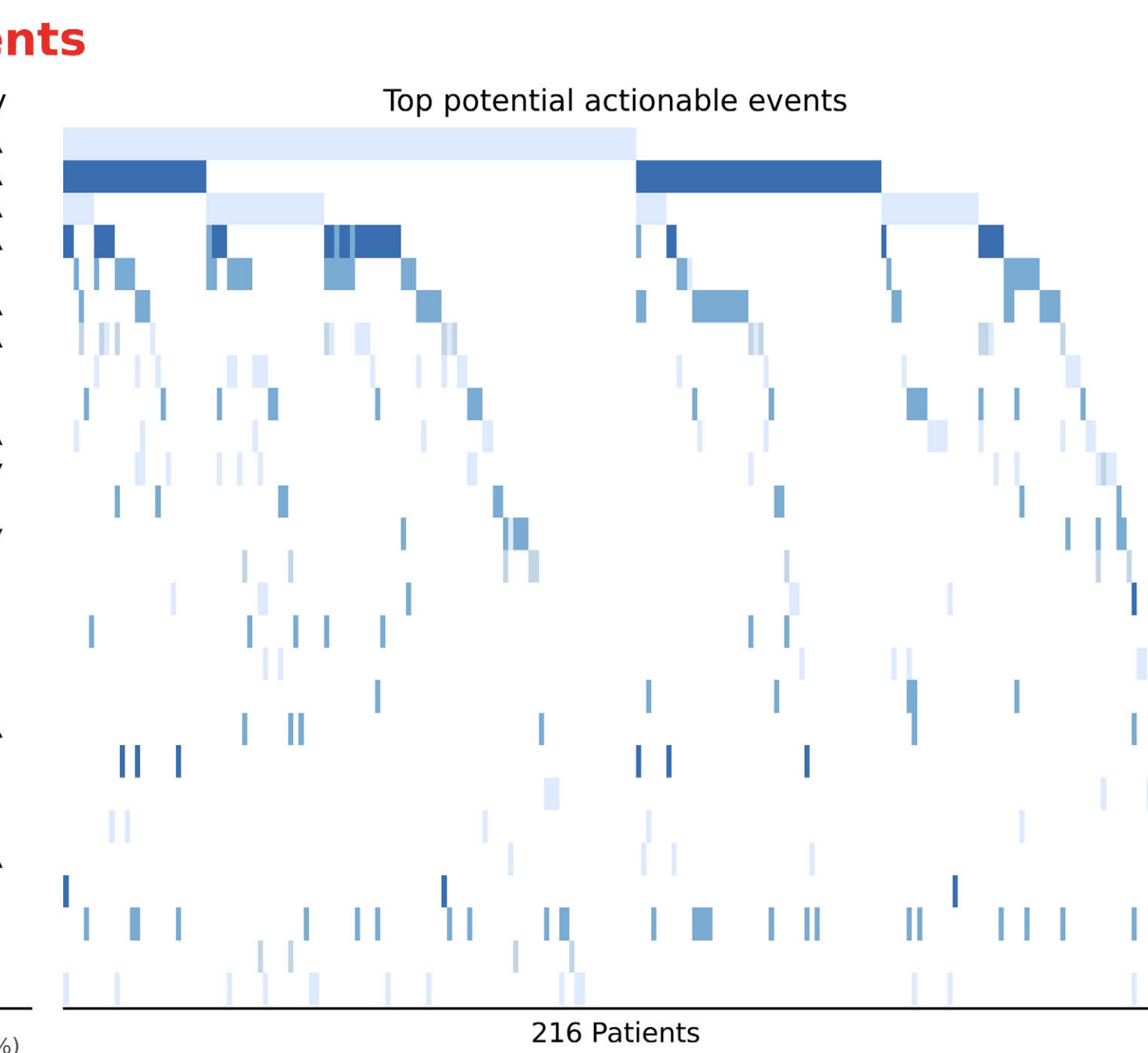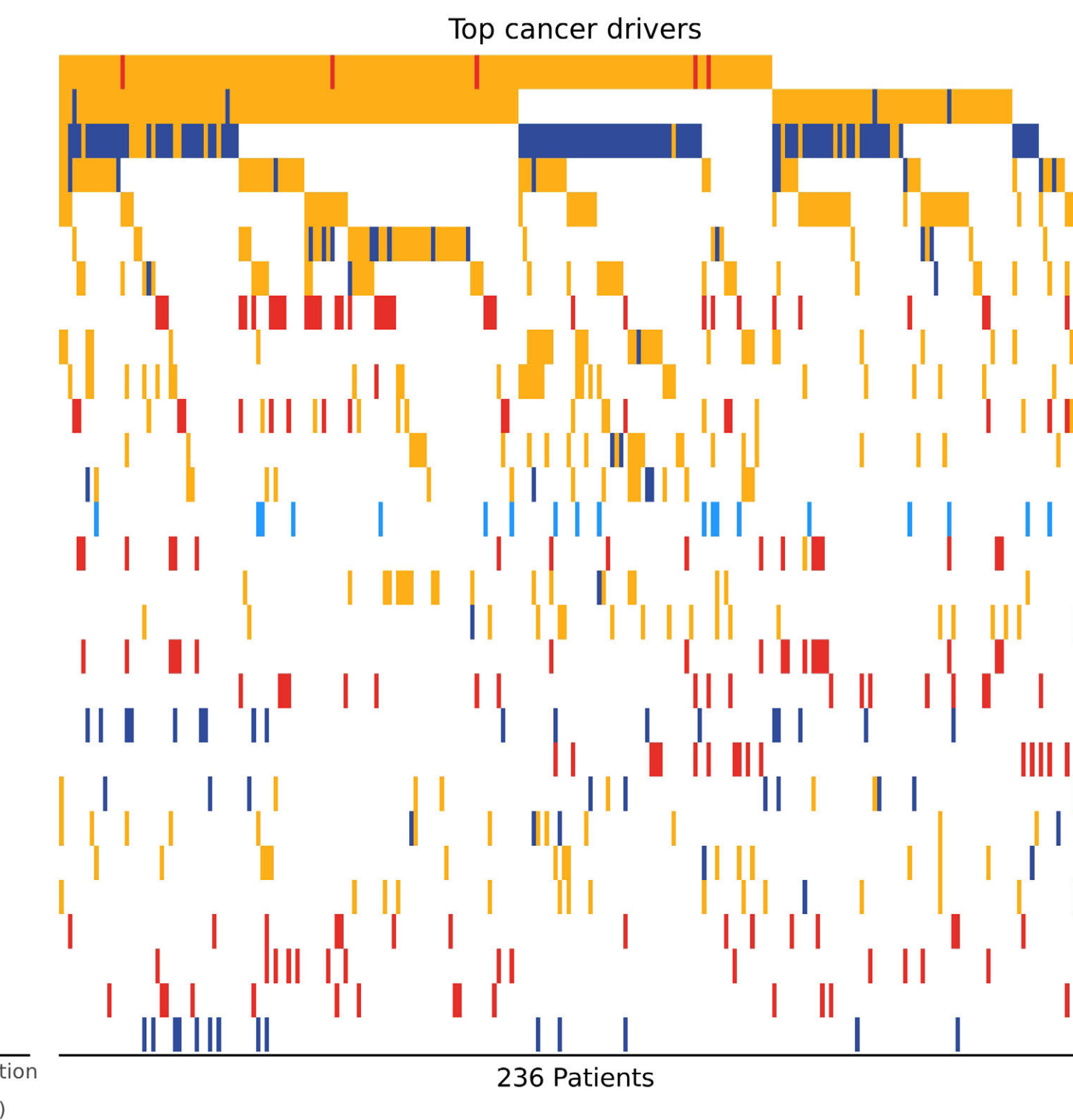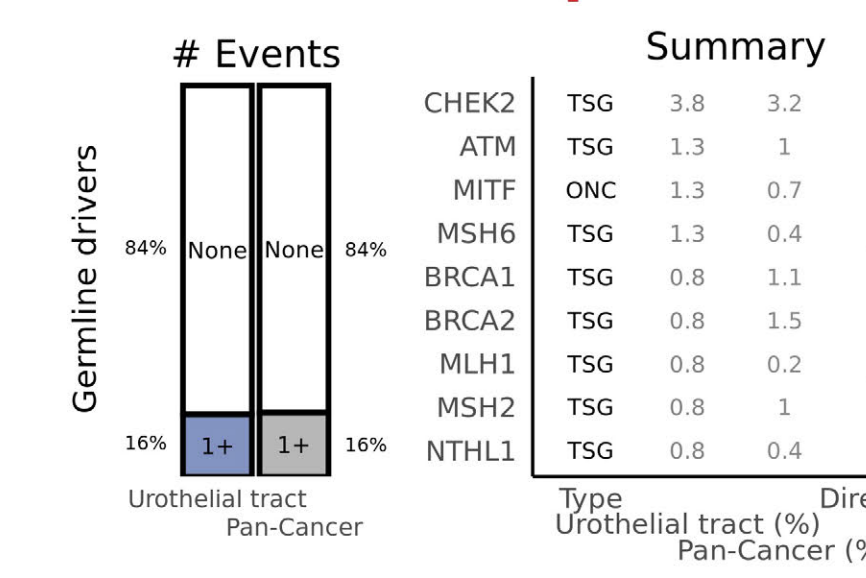| | Thymus | Pan-Cancer |
|---|---|---|
| None | 38% | None 18% |
| Oth | 6% | Oth 14% |
| Exp | | Exp 5% |
| Off | 31% | Off 28% |
| FDA | 25% | FDA 36% |

| Gene | Thymus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 25 | 24 | |
| TMB High | 25 | 21 | |
| KIT | 12 | 1.1 | ▲ |
| BRCA2 | 6.2 | 2.4 | |
| CHEK2 | 6.2 | 3 | |
| ERBB3 | 6.2 | 0.5 | ▲ |
| FGFR2 | 6.2 | 1.1 | ▲ |
| HRAS | 6.2 | 0.6 | ▲ |

Top potential actionable events — 10 Patients

Legend: ■ FDA Approved ■ Drug Repurposing ■ Other

## Germline Predisposition

### # Events / Summary

**Germline drivers**

| | Thymus | Pan-Cancer |
|---|---|---|
| None | 81% | None 84% |
| 1+ | 19% | 1+ 16% |

| Gene | Type | Thymus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRCA2 | TSG | 6.2 | 1.5 | ▲ |
| MUTYH | TSG | 6.2 | 1.9 | ▲ |
| NTHL1 | TSG | 6.2 | 0.4 | ▲ |

Top potential germline drivers — 3 Patients

Legend: ■ SMALL_VARIANT

## WGS vs Panel Coverage

Legend: ■ FDA Approved ■ Drug Repurposing ■ Other ☐ None

### Highest evidence level treatment option identified by test strategy

| Test strategy | | | | |
|---|---|---|---|---|
| WGS | 4 | 5 | 1 | 6 |
| Comprehensive 521 gene panel | 4 | 5 | 1 | 6 |
| Targeted 50 gene panel | 2 | 1 | 2 | 11 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | |
|---|---|---|---|---|
| WGS | 0.25 | 0.31 | 0.38 | 1 |
| Comprehensive 521 gene panel | 0.25 | 0.31 | 0.38 | 1 |
| Targeted 50 gene panel | | 0.31 | 0.5 | |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved | Drug Repurposing | Experimental/Other Guidelines | Other

(no events shown)

### Top missed events by Targeted Panel vs WGS

| | FDA Approved | Drug Repurposing |
|---|---|---|
| TMB High | 4 | |
| Small Variant | | 3 |

Experimental/Other Guidelines | Other

| | Other |
|---|---|
| Small Variant | 1 |

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Thyroid Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 29 |
| RNASeq | 19 |
| Age, Sex | 20 |
| Biopsy site | 19 |
| Pretreatment | 16 |
| Treatment | 13 → |
| Response | 8 → |

**Patients with treatment and response data**

Post-biopsy treatment / Responders

| | | |
|---|---|---|
| Chemo | 2 | 0 |
| Multiple | 0 | 0 |
| Targeted | 6 | 1 (17%) |
| Hormonal | 0 | 0 |
| Immuno | 0 | 0 |
| Radio | 0 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Thyroid / Pan-Cancer

| | Thyroid | Pan-Cancer |
|---|---|---|
| TMB High | 3% | 21% |
| MSI High | 0% | 2% |
| WGD | 38% | 56% |
| Diploid Proportion | 48% | 34% |
| GIE HLA LOH | 21% | 19% |
| GIE Overall | 24% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

**Tumor purity** 54% / 55%

**Clonal mutation fraction** 93% / 95%

**Tumor mutational burden** 1.8 / 4.2 — High 3% / 21%

TMB per Megabase

### Variant types

| SNV | INDEL | Structural | MNV |
|---|---|---|---|
| 10,846 / 4,541 | 983 / 356 | 183 / 36 | 92 / 30 |

Number of variants vs Quantile

**Telomere Length** 0.65 / 0.82 — Log2 (Tumor/Germline length)

**VDJ CDR3 Sequences** 6 / 6 — Log2 (CDR3 + 1)

**Microsatellite instability** 0.051 / 0.15 — Instable 0% / 2% — MS indels per megabase

**Mean genome ploidy** 2 / 2.6

**Aneuploidy Score** 9 / 16

**% Copy number alteration** 40% / 54%

**% Genome LOH** 20% / 24%

## Processes Underlying Mutations

| | |
|---|---|
| APOBEC | 28% |
| DNA damage repair | 15% |
| Chemical exposure | 8% |
| Ageing | 8% |
| Tobacco | 2% |
| UV light | 1% |
| Unknown | 39% |

Thyroid 29 Patients

Pan-Cancer 6790 Patients

Thyroid

Made with bioRender

## Copy Number Alteration Profile

Chromosome circle plot — genes labeled: AR, CDKN2C, LRP1B, PRKAR1A, NF1, NAALADL2, KIT, PDGFRA, CCND3, CDK6, CCND2, CHD4, KRAS, LINC01001, CDKN2A

## Cancer Driver Landscape

### # Events / Summary — Top cancer drivers

**Somatic drivers:** None 7% / 14%; 6+ 44%; 1-5 79%

**Oncogenes:** None 17% / 18%; 3+ 32%; 1-2 66% / 50%

**TSGs:** None 21%; 3+ 31% / 61%; 1-2 48% / 33%

| Gene | Type | Thyroid (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CDKN2A | TSG | 38 | 25 | ▲ |
| TERT | ONC | 34 | 13 | ▲ |
| RET | ONC | 28 | 0.3 | ▲ |
| TP53 | ONC | 24 | 55 | ▼ |
| BRAF | ONC | 17 | 6.2 | ▲ |
| NF1 | ONC | 10 | 5 | ▲ |
| PIK3CA | ONC | 10 | 13 | |
| RBM10 | TSG | 10 | 1.4 | ▲ |
| CDKN2C | TSG | 6.9 | 0.4 | ▲ |
| LRP1B | TSG | 6.9 | 2.1 | ▲ |
| NRAS | ONC | 6.9 | 2.8 | |
| PRKAR1A | TSG | 6.9 | 0.2 | ▲ |
| STK11 | TSG | 6.9 | 4.1 | |
| AKT1 | ONC | 3.4 | 1.6 | |
| AR | ONC | 3.4 | 5.6 | |
| ARID1A | TSG | 3.4 | 6 | |
| ARID2 | TSG | 3.4 | 1.8 | |
| ATM | ONC | 3.4 | 2.9 | |
| AXIN1 | TSG | 3.4 | 0.6 | ▲ |
| BAP1 | TSG | 3.4 | 2.7 | |
| BCOR | TSG | 3.4 | 0.7 | ▲ |
| CCND2 | ONC | 3.4 | 1.1 | ▲ |
| CCND3 | ONC | 3.4 | 0.8 | ▲ |
| CDK6 | ONC | 3.4 | 0.9 | ▲ |
| CHD4 | ONC | 3.4 | 1.2 | |
| CREBBP | TSG | 3.4 | 1.9 | |
| DDX3X | TSG | 3.4 | 0.6 | ▲ |
| DNMT3A | TSG | 3.4 | 0.8 | ▲ |
| ETV6_NTRK3 | | 3.4 | 0 | ▲ |

26 Patients

Legend: AMPLIFICATION / DELETION / MUTATION / FUSION

## Potentially Actionable Events

### # Events / Summary — Top potential actionable events

**Actionable:** None 17% / 18%; 3+ 17% / 26%; 1-2 66% / 56%

**Best treatment option:** None 17%; Oth 10% / 14%; Exp 5%; Off 45% / 28%; FDA 28% / 36%

| Gene | Thyroid (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| CDKN2A | 38 | 24 | |
| RET | 31 | 0.2 | ▲ |
| BRAF | 17 | 5.9 | |
| PIK3CA | 10 | 13 | |
| NRAS | 6.9 | 2.6 | |
| AKT1 | 3.4 | 1.4 | |
| ATM | 3.4 | 3.5 | |
| CHEK2 | 3.4 | 3 | |
| ETV6 - NTRK3 fusion | 3.4 | 0 | ▲ |
| HRAS | 3.4 | 0.6 | ▲ |
| KDM5C | 3.4 | 0.6 | ▲ |
| KMT2D | 3.4 | 2.9 | |
| KRAS | 3.4 | 14 | ▼ |
| NF1 | 3.4 | 0.4 | ▲ |
| TMB High | 3.4 | 21 | ▼ |

24 Patients

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

**Germline drivers:** None 86% / 84%; 1+ 14% / 16%

| Gene | Type | Thyroid (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CHEK2 | TSG | 3.4 | 3.2 | |
| MUTYH | TSG | 3.4 | 1.9 | |
| PMS2 | TSG | 3.4 | 0.5 | ▲ |
| RET | ONC | 3.4 | 0 | ▲ |

Top potential germline drivers — 4 Patients

Legend: SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other / None

### Highest evidence level treatment option identified by test strategy

| Strategy | FDA | Drug Repurposing | Exp | Other | None |
|---|---|---|---|---|---|
| WGS | 8 | 13 | 2 | 1 | 5 |
| Comprehensive 521 gene panel | 7 | 13 | 2 | 2 | 5 |
| Targeted 50 gene panel | 6 | 13 | 2 | | 8 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Strategy | | | | Total |
|---|---|---|---|---|
| WGS | 0.28 | 0.62 | 0.62 | 1.7 |
| Comprehensive 521 gene panel | 0.24 | 0.62 | 0.48 | 1.4 |
| Targeted 50 gene panel | 0.21 | 0.48 | 0.38 | 1.1 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

- FDA Approved: Fusion 1
- Drug Repurposing:
- Experimental/Other Guidelines: Partial CN Loss 1
- Other: Partial CN Loss 3; Full CN Loss 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

- FDA Approved: Fusion 1; TMB High 1
- Drug Repurposing: Small Variant 4
- Experimental/Other Guidelines: Full CN Gain 2; Partial CN Loss 1
- Other: Partial CN Loss 3; Small Variant 2; Full CN Loss 1; Splice Site 1

Number of Missed Events

## Panel annotations and abbreviations

Cohort Metadata: WGS - whole genome sequencing, RNASeq - RNA Sequencing, Chemo - Chemotherapy, Targeted - Targeted Therapy, Hormonal - Hormonal Therapy, Immuno - Immunotherapy, Radio - Radiotherapy. Treatments - some samples received multiple types of treatment. Patients have both pre and post biopsy treatment available. Responders - Complete or partial response based on RECIST criteria.

Tumor Characteristics: TMB - tumor mutational burden, MSI - microsatellite instable, WGD - whole genome doubling, GIE - genetic immune escape, HLA - human leukocyte antigen, LOH - loss of heterozygosity, HRD - homologous recombination deficiency.

Mutational Landscape: SNV - single nucleotide variant, INDEL - insertion or deletion, Structural - structural variant, MNV - multiple nucleotide variant, CDR - Complementarity-determining regions.

Processes Underlying Mutations: Processes estimated based on single base substitutions and trinucleotide contexts. Signatures were fit using deconstructSigs in R with cosmic version 3.4 and grouped based on proposed aetiology.

Copy Number Alteration Profile: Inner ring shows the percentage of tumours with homozygous deletion (dark blue), LOH and significant loss (copy number < 0.6× sample ploidy; blue) and near copy neutral LOH (light blue). Outer ring shows (percentage of tumours with high level amplification (>3× sample ploidy; dark red); moderate amplification (>2× sample ploidy; red) and low level amplification (>1.4 × sample ploidy; light red). Frequently observed high-level driver gene amplifications (red) and homozygous deletions (blue).
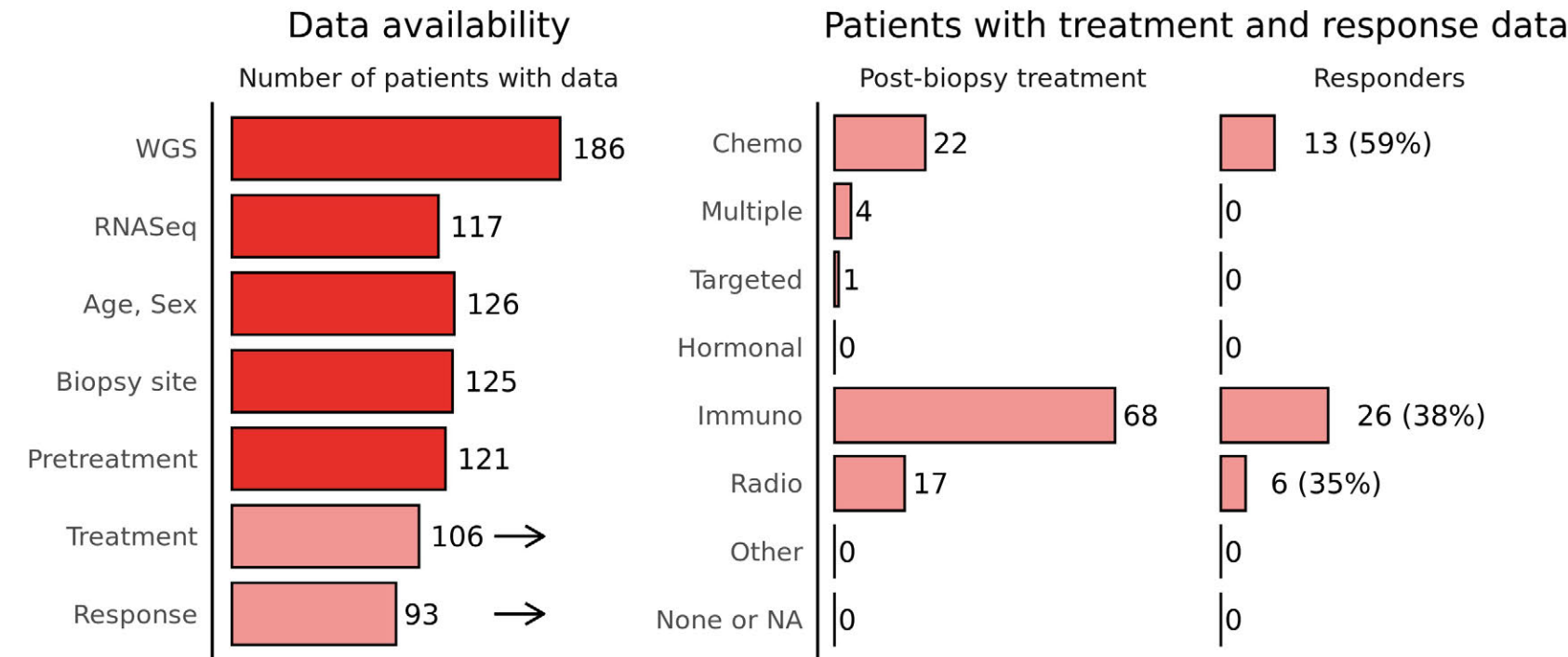
Cancer Driver Landscape, Germline Disposition: Events - events per tumor, TSG - tumor suppressor gene, ONC - oncogene. Summary %'s based on all samples, oncoplots only show samples with atleast 1 event.

Potentially Actionable Events: References Jackson Clinical Knowledgebase database. # Events: FDA - FDA approved, Off - Drug Repurposing, Exp - Experimental/Other Guidelines, Oth - Any other event. TMB high - tumor mutational burden > 10 mutations per megabase, MSI high - > 4 microsatellite inserts per megabase, Rest * - All remaining potentially actionable events.

Acronym: THCA

DOIDs included: 1781

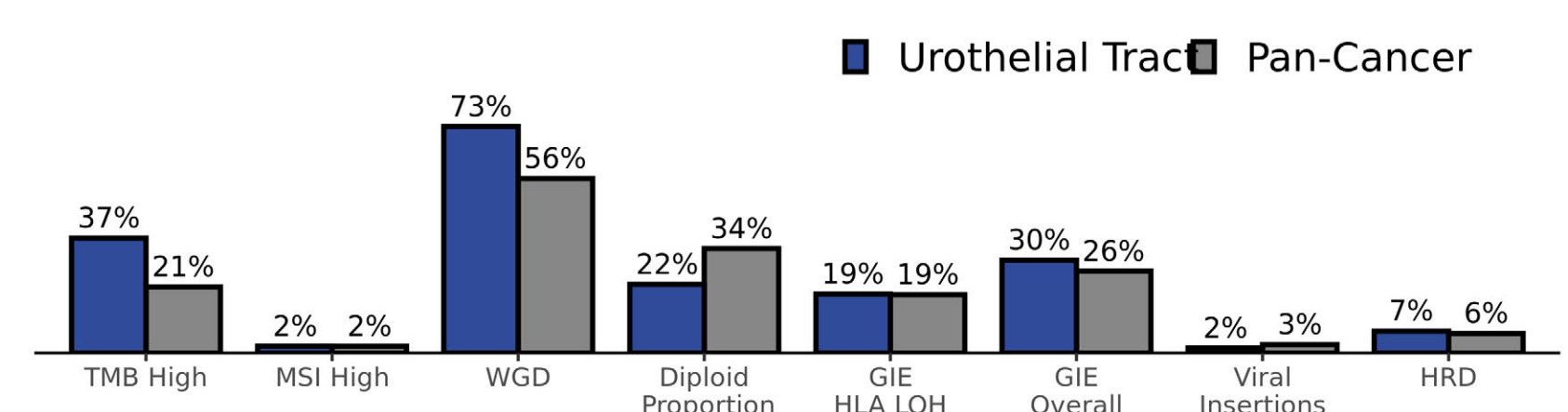Date created from database: 2024-07-06

WGS vs Panel Coverage Summary: In-silico coverage study comparing WGS to comprehensive and targeted panels across various genomic biomarkers. WGS actionable biomarkers identified by the Jackson Clinical Knowledgebase (CKB) used as a baseline, and panel coverage determined by rules below:
- Signatures: TMB High and MSI High captured by comprehensive panel (no HRD); only MSI High covered by targeted panel.
- Small variants/splice sites: Coverage measured by comparing genomic coordinates of events to panel BED input files.
- Copy number: Events for panel genes with: min copy number < 0.5 or max copy number > 6 assumed covered.
- Other events: Fusions, HMZ (Homozygous) Distruptions, Viral inserts, HLA type assumed not captured by panels.
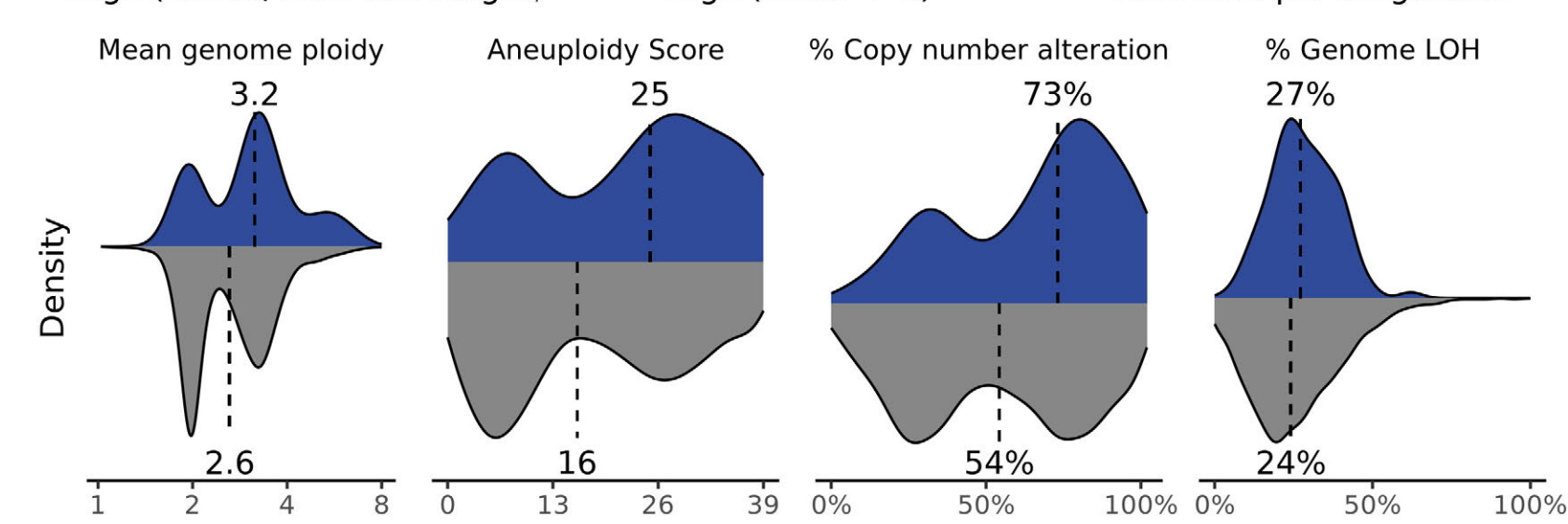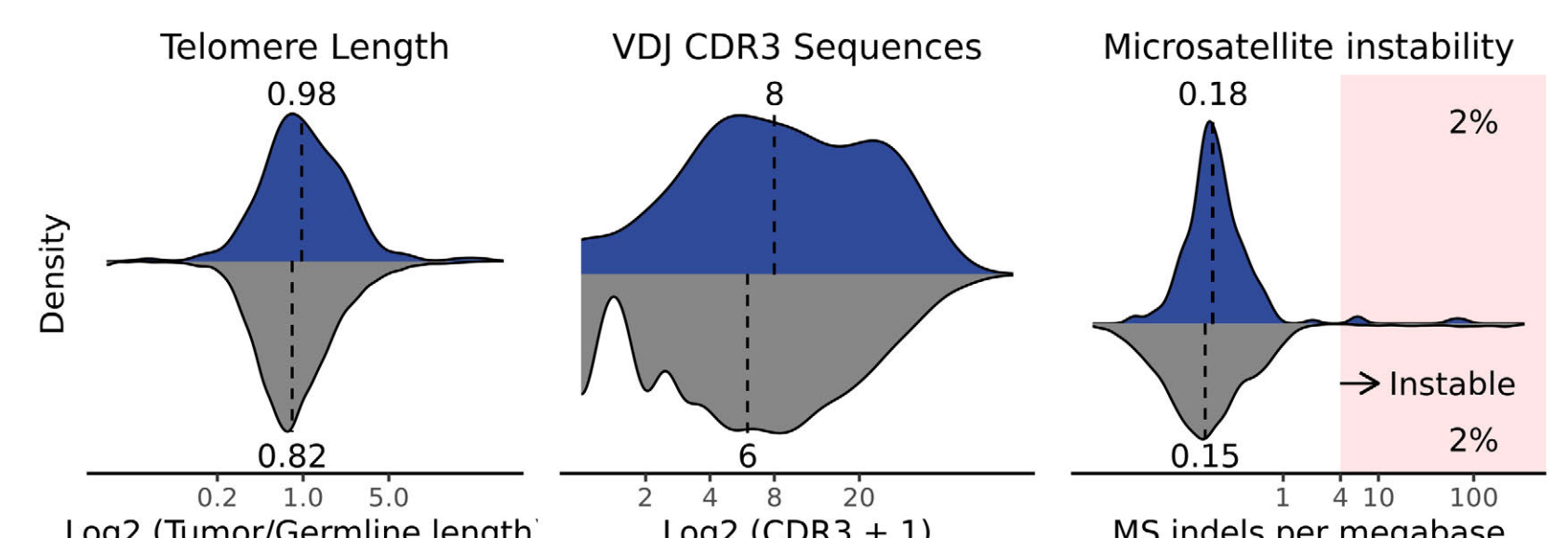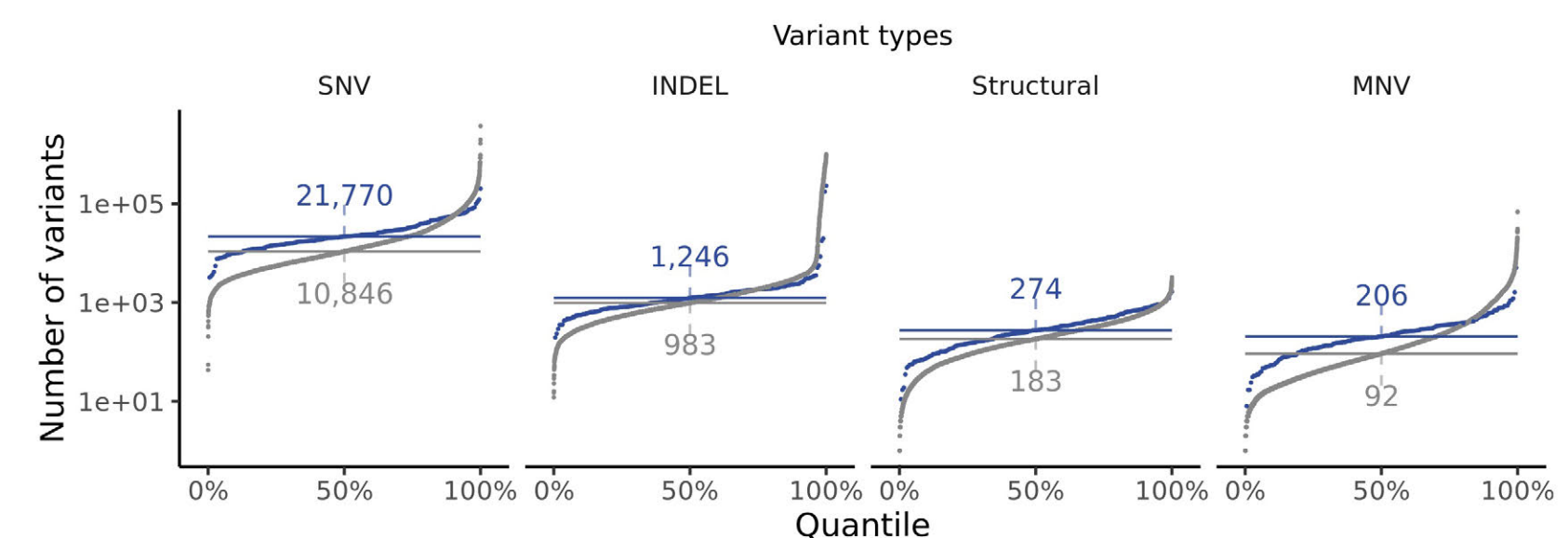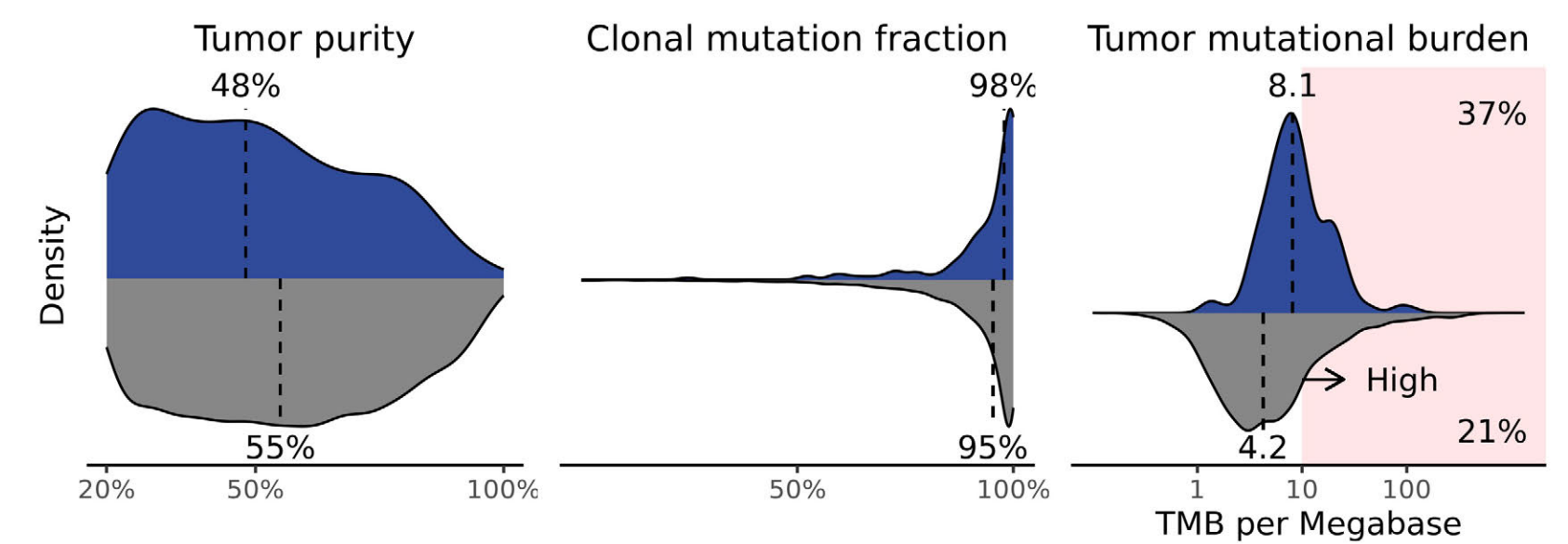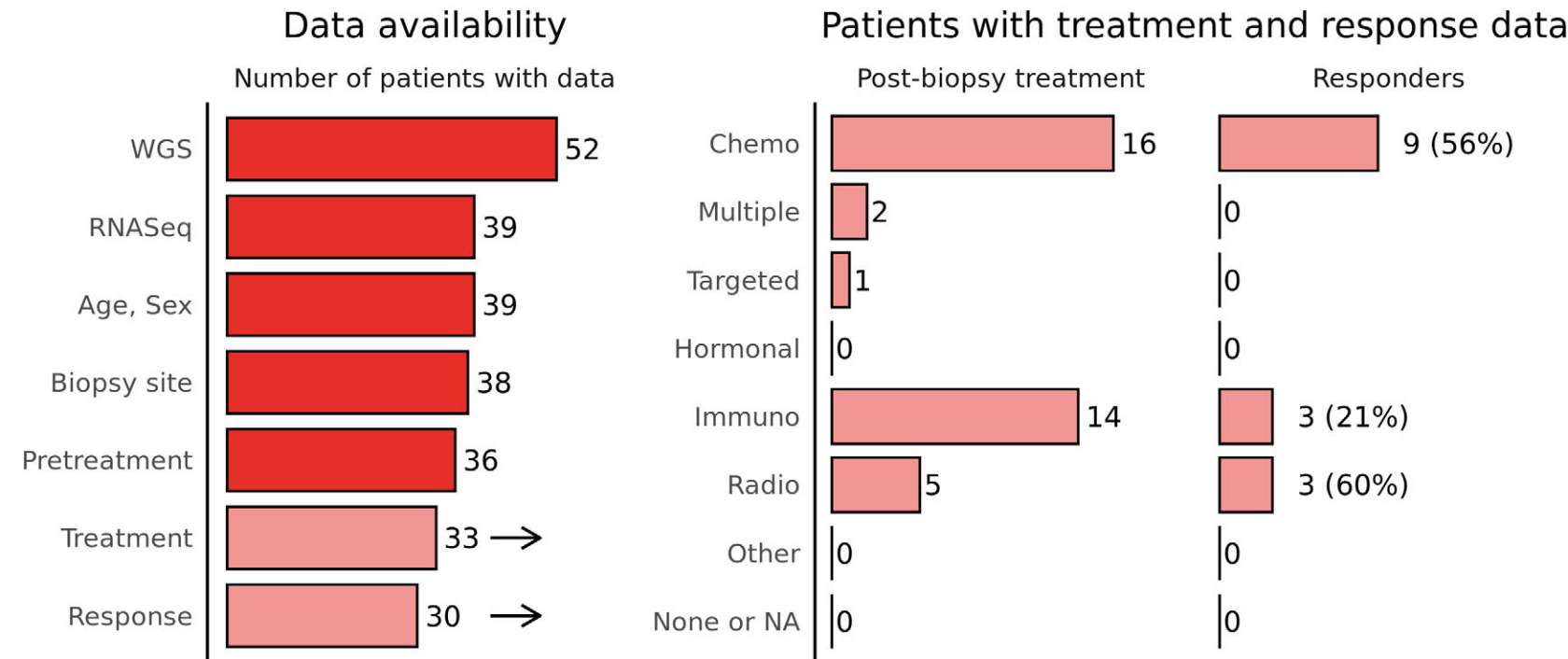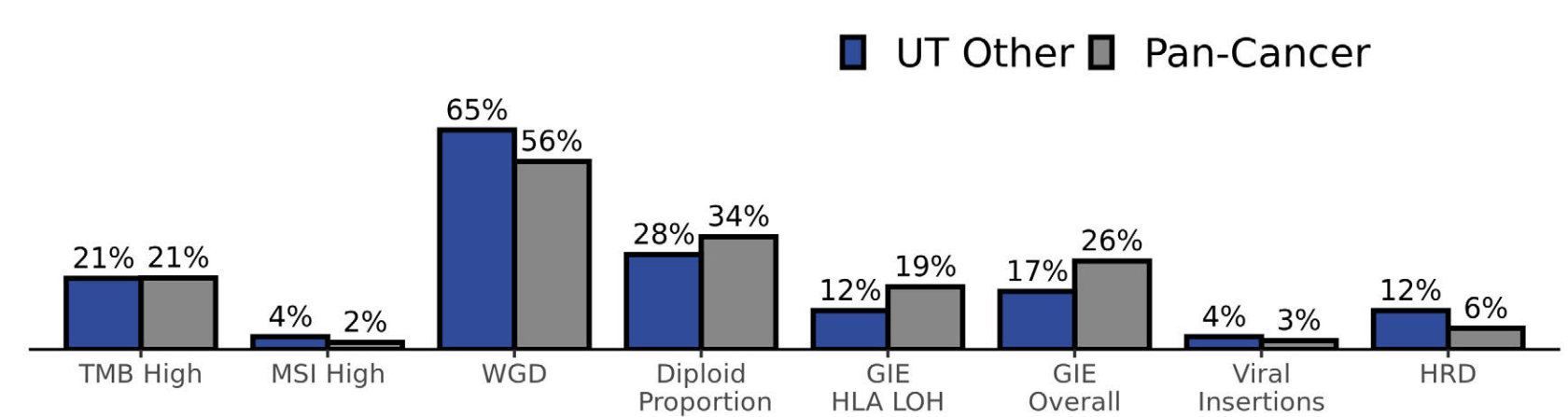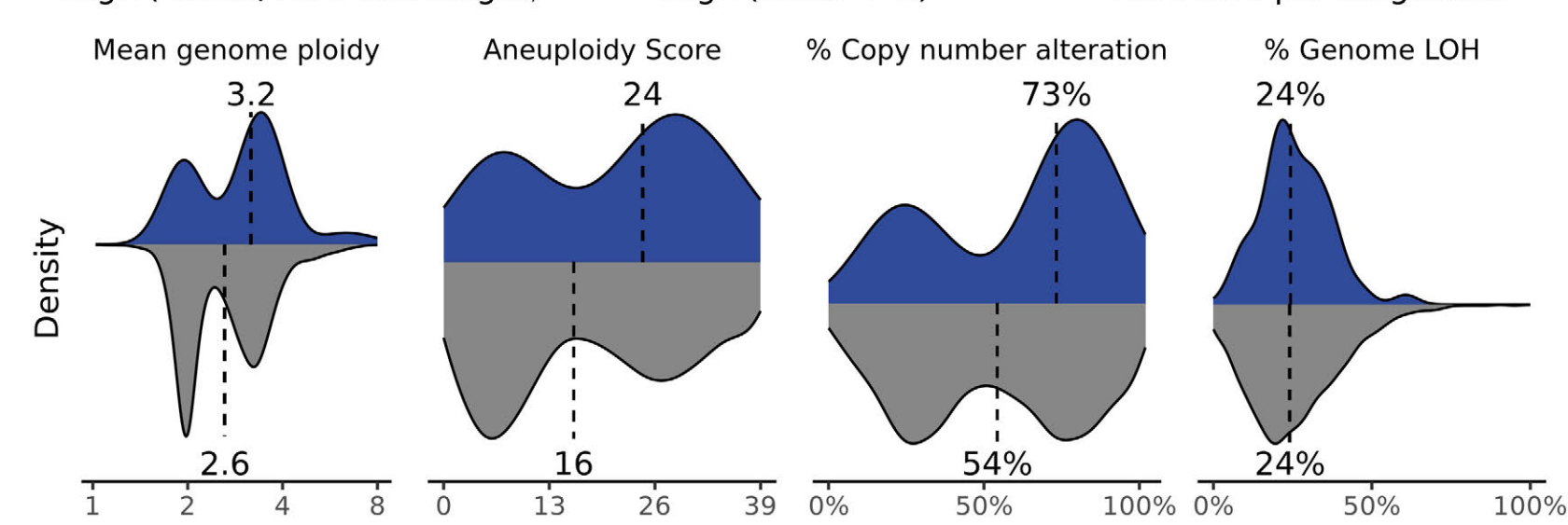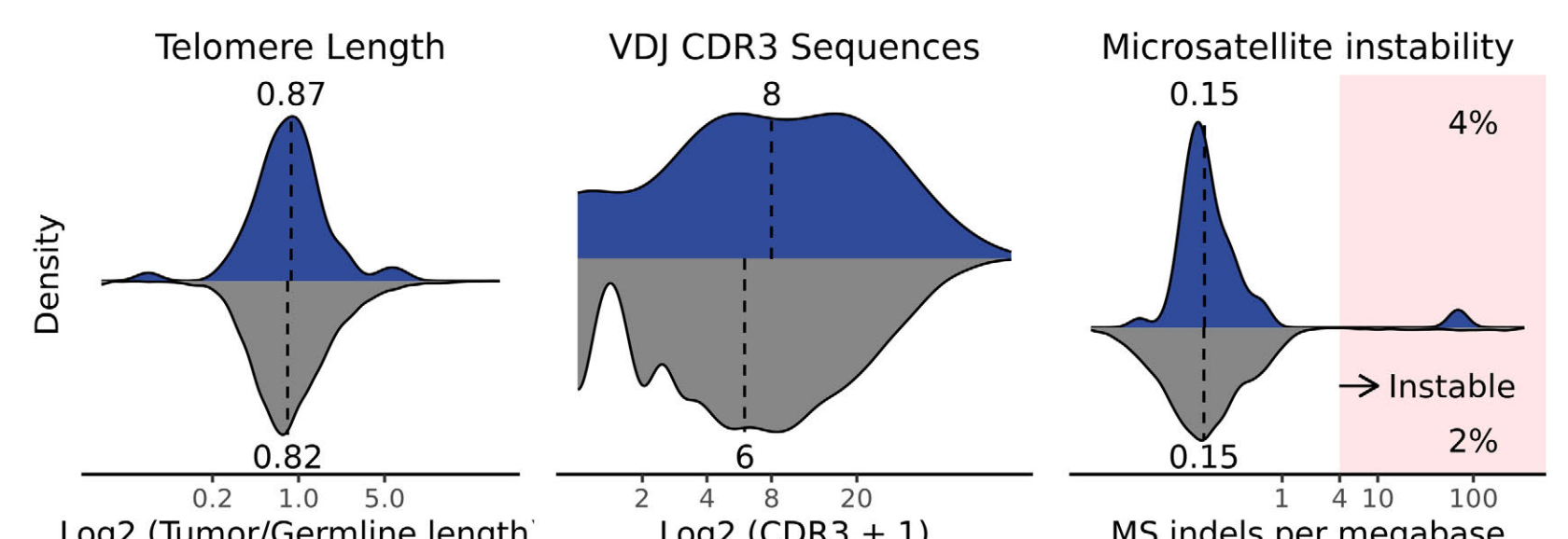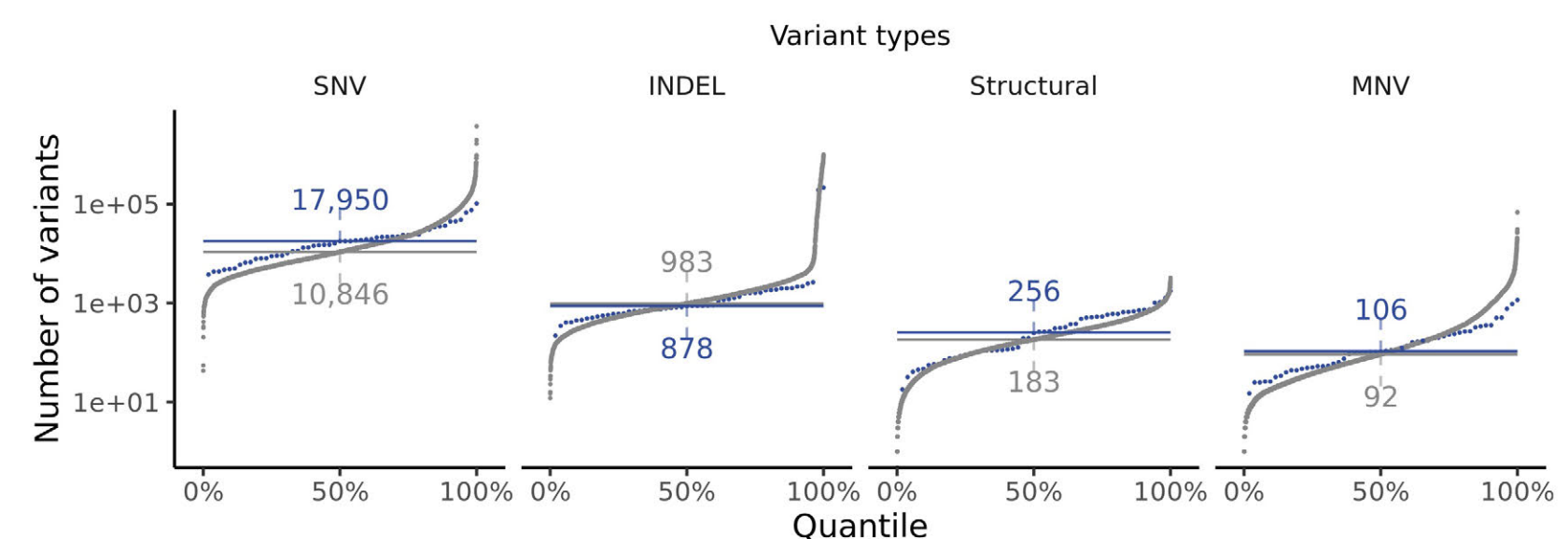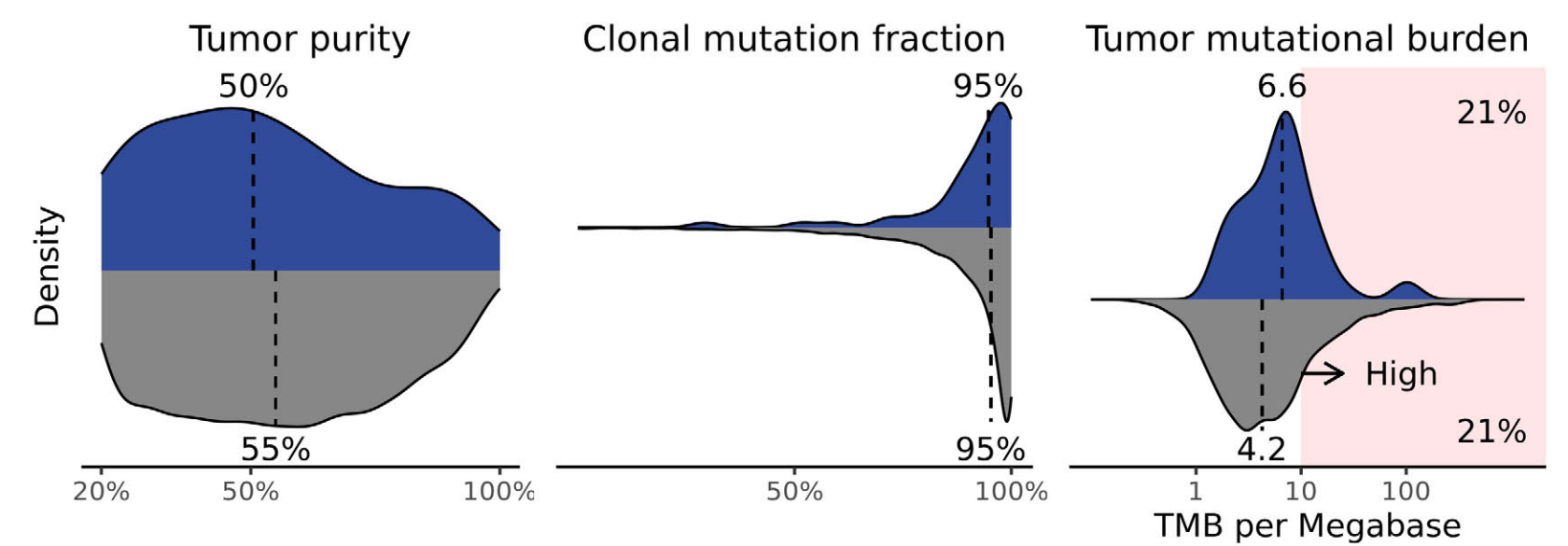** See documentation for further details on the WGS vs Panel coverage study.

# The Genomic And Actionability Landscape Of Urothelial Tract Cancer

## Cohort Metadata

### Data availability — Number of patients with data

| | |
|---|---|
| WGS | 239 |
| RNASeq | 157 |
| Age, Sex | 166 |
| Biopsy site | 164 |
| Pretreatment | 158 |
| Treatment | 140 → |
| Response | 124 → |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 39 | 23 (59%) |
| Multiple | 6 | 0 |
| Targeted | 2 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 82 | 29 (35%) |
| Radio | 22 | 9 (41%) |
| Other | 0 | 0 |
| None or NA | 0 | |

## Processes Underlying Mutations

- APOBEC: 38%
- DNA damage repair: 17%
- Chemical exposure: 13%
- Ageing: 5%
- Tobacco: 4%
- UV light: 4%
- Unknown: 19%

Urothelial tract
239 Patients

Pan-Cancer
6790 Patients

Urothelial tract

Made with bioRender

## Tumor Characteristics

Urothelial tract / Pan-Cancer

| | Urothelial tract | Pan-Cancer |
|---|---|---|
| TMB High | 33% | 21% |
| MSI High | 3% | 2% |
| WGD | 71% | 56% |
| Diploid Proportion | 23% | 34% |
| GIE HLA LOH | 17% | 19% |
| GIE Overall | 27% | 26% |
| Viral Insertions | 2% | 3% |
| HRD | 8% | 6% |

## Mutational Landscape

- Tumor purity: 48% / 55%
- Clonal mutation fraction: 97% / 95%
- Tumor mutational burden: 7.9 / 4.2 — High 33% / 21% — TMB per Megabase

### Variant types

| | Urothelial | Pan-Cancer |
|---|---|---|
| SNV | 20,720 | 10,846 |
| INDEL | 1,164 | 983 |
| Structural | 269 | 183 |
| MNV | 193 | 92 |

- Telomere Length: 0.92 / 0.82 — Log2 (Tumor/Germline length)
- VDJ CDR3 Sequences: 8 / 6 — Log2 (CDR3 + 1)
- Microsatellite instability: 0.17 / 0.15 — Instable 3% / 2% — MS indels per megabase
- Mean genome ploidy: 3.2 / 2.6
- Aneuploidy Score: 25 / 16
- % Copy number alteration: 73% / 54%
- % Genome LOH: 26% / 24%

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events (Somatic drivers)

Somatic drivers: 82% 6+, 18% 1-5
Oncogenes: 5% None, 59% 3+, 36% 1-2
TSGs: 87% 3+, 13% 1-2

| Gene | Type | Urothelial tract (%) | Pan-Cancer (%) |
|---|---|---|---|
| TERT | ONC | 68 | 13 |
| TP53 | TSG | 67 | 55 |
| CDKN2A | TSG | 50 | 25 |
| KDM6A | TSG | 25 | 3.7 |
| KMT2D | TSG | 22 | 2.9 |
| RB1 | TSG | 21 | 11 |
| ARID1A | TSG | 17 | 6 |
| SOX4 | ONC | 15 | 0.7 |
| FGFR3 | ONC | 15 | 1.3 |
| PIK3CA | ONC | 14 | 13 |
| ERBB2 | ONC | 13 | 5.7 |
| ELF3 | TSG | 11 | 1.3 |
| TSC1 | TSG | 8.8 | 1.1 |
| AHR_AHR | ONC | 8.4 | 0.4 |
| CCND1 | ONC | 8.4 | 5.6 |
| CDKN1A | TSG | 8.4 | 0.5 |
| CREBBP | TSG | 8.4 | 1.9 |
| FGF3 | ONC | 7.9 | 5.2 |
| RYR1 | ONC | 7.9 | 1.5 |
| LRP1B | TSG | 7.5 | 2.1 |
| MDM2 | ONC | 7.1 | 3.3 |
| PTEN | TSG | 7.1 | 14 |
| STAG2 | TSG | 7.1 | 0.9 |
| ZFP36L1 | TSG | 7.1 | 0.7 |
| FBXW7 | TSG | 6.7 | 2.8 |
| RAF1 | ONC | 6.7 | 0.6 |
| CCNE1 | ONC | 5.9 | 2.4 |
| CRYBG1 | ONC | 5.9 | 5.9 |
| FHIT | TSG | 5.9 | 4.3 |

Top cancer drivers — 236 Patients

Legend: AMPLIFICATION / DELETION / MUTATION / FUSION

## Potentially Actionable Events

### # Events

Actionable: 10% None, 42% 3+, 48% 1-2
Best treatment option: 10% None, 19% Oth, 26% Off, 43% FDA
Pan-Cancer: 18% None, 14% Oth, 5% Exp, 28% Off, 36% FDA

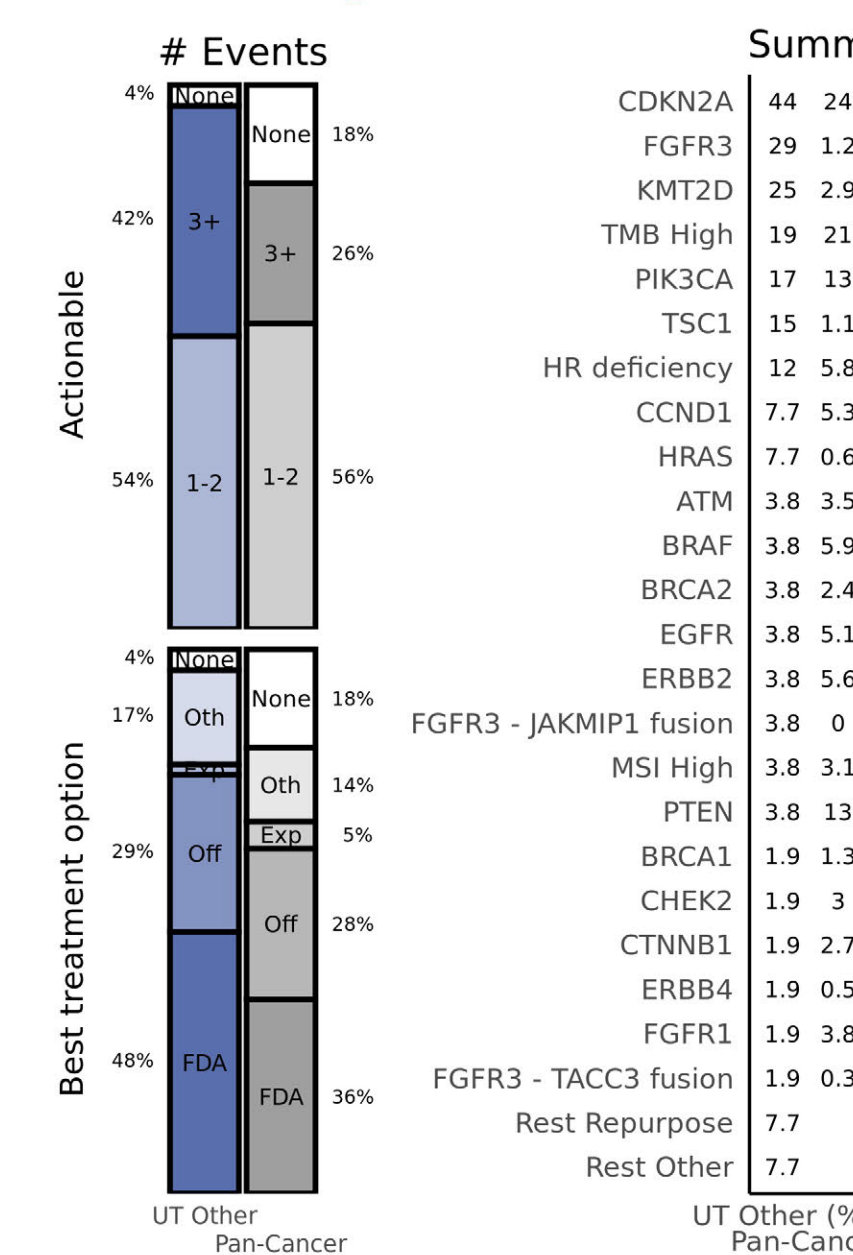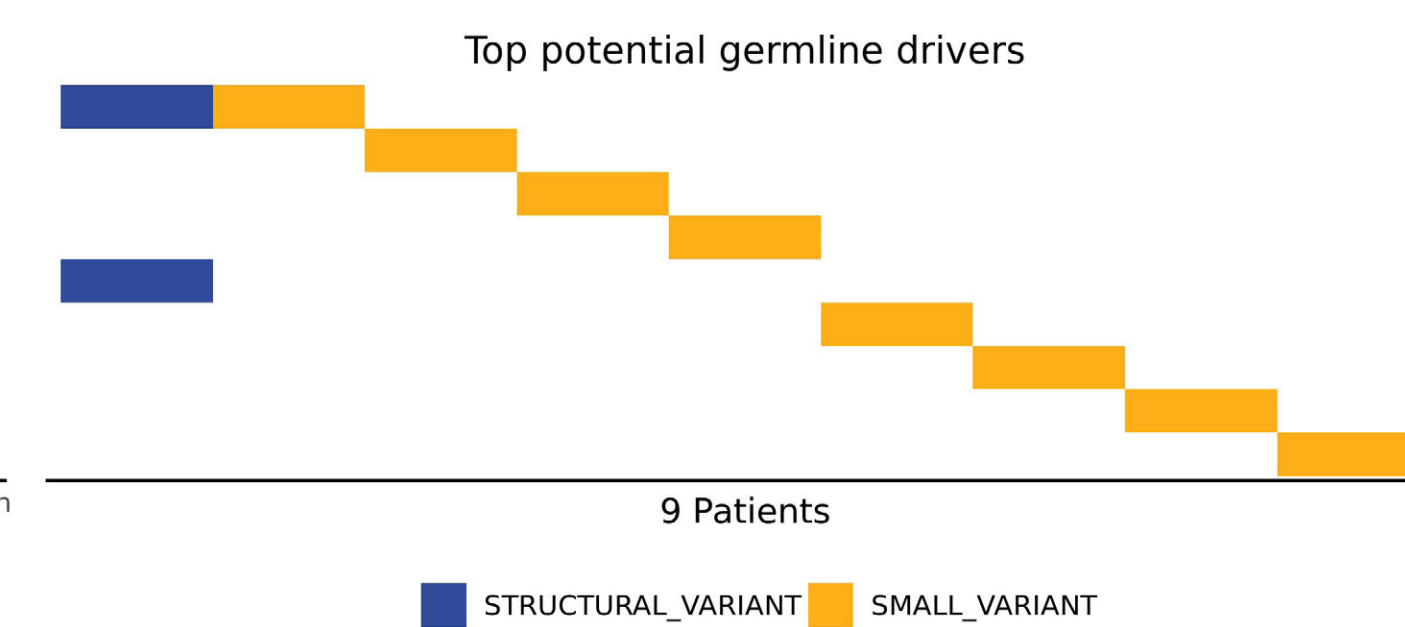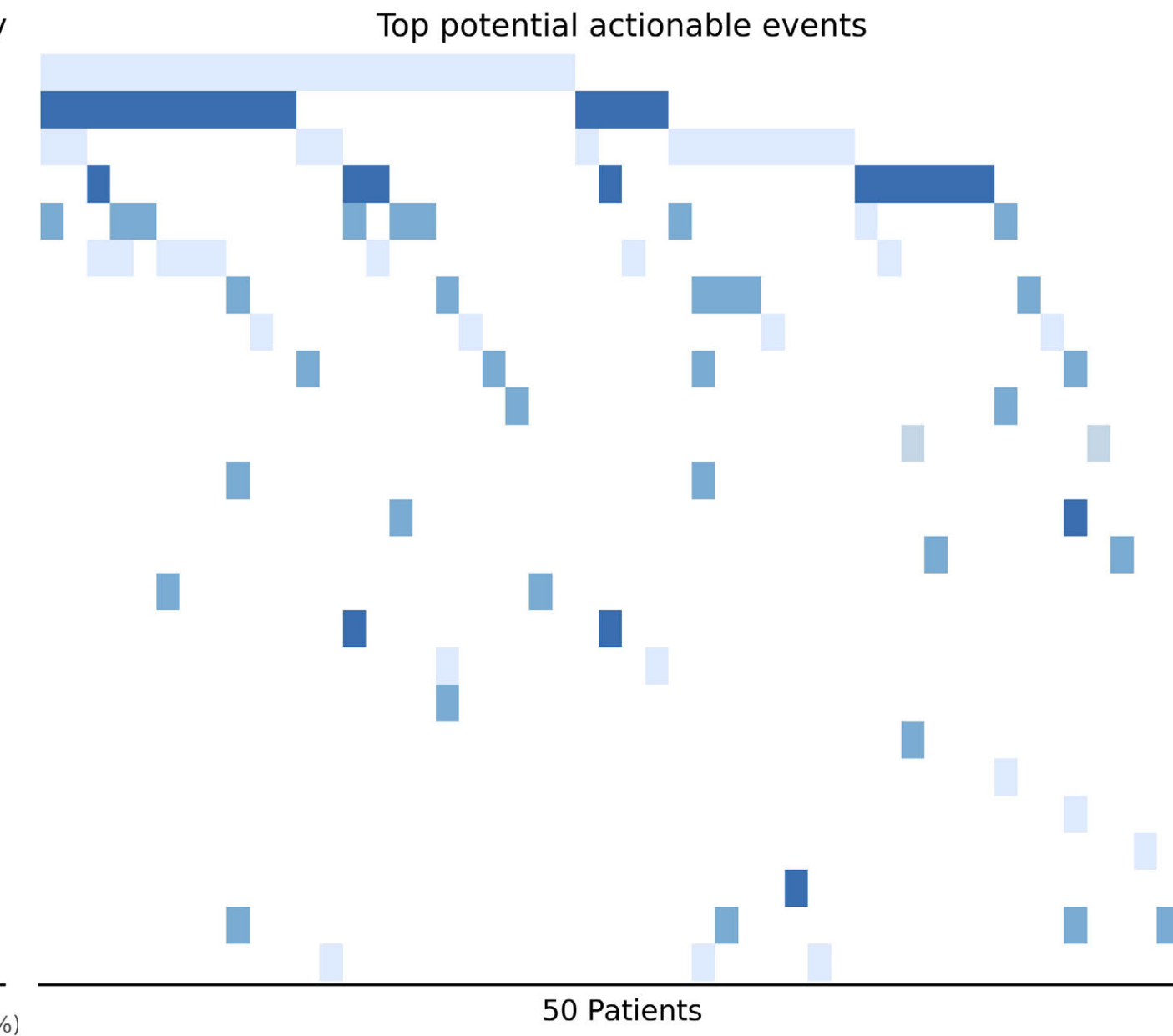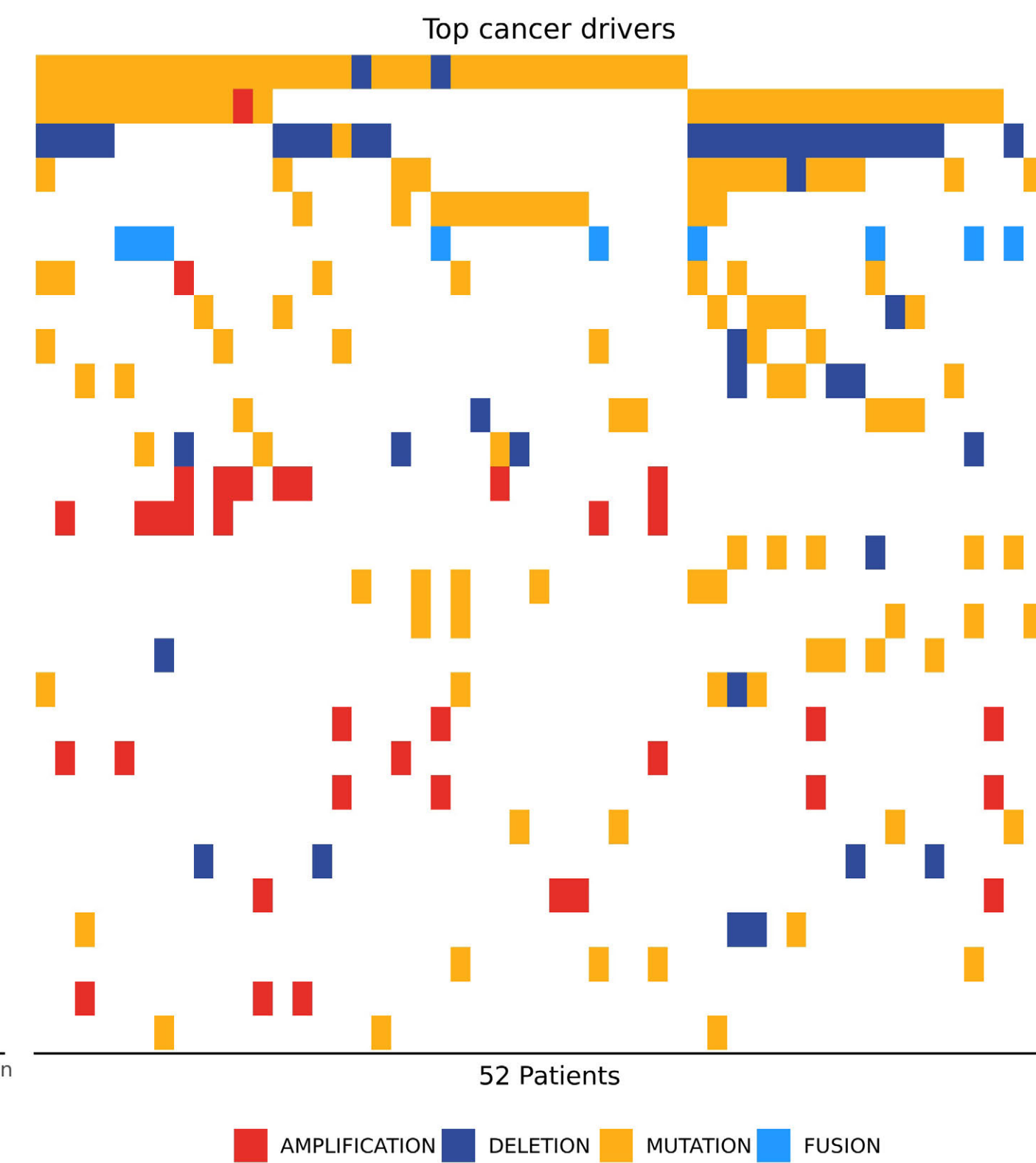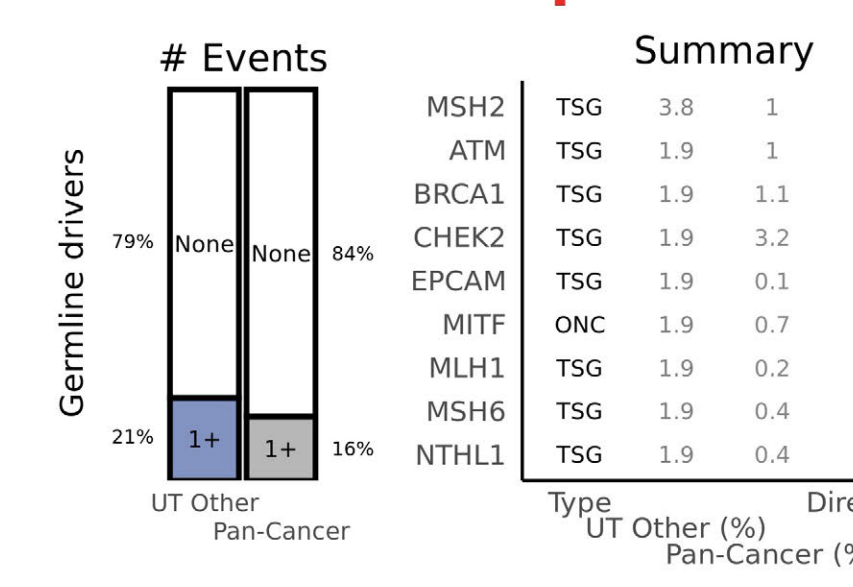| | Urothelial tract (%) | Pan-Cancer (%) |
|---|---|---|
| CDKN2A | 47 | 24 |
| TMB High | 32 | 21 |
| KMT2D | 23 | 2.9 |
| FGFR3 | 14 | 1.2 |
| PIK3CA | 14 | 13 |
| ERBB2 | 13 | 5.6 |
| TSC1 | 8.4 | 1.1 |
| CCND1 | 7.9 | 5.3 |
| HR deficiency | 7.5 | 5.8 |
| RAF1 | 6.7 | 0.4 |
| PTEN | 6.3 | 13 |
| ATM | 4.2 | 3.5 |
| KRAS | 4.2 | 14 |
| BRAF | 3.3 | 5.9 |
| EGFR | 3.3 | 5.1 |
| CHEK2 | 2.9 | 3 |
| FGFR1 | 2.9 | 3.8 |
| BRCA2 | 2.5 | 2.4 |
| HRAS | 2.5 | 0.6 |
| MSI High | 2.5 | 3.1 |
| NF2 | 2.5 | 1.6 |
| CTNNB1 | 2.1 | 2.7 |
| ERBB3 | 1.7 | 0.5 |
| Rest FDA | 1.7 | |
| Rest Repurpose | 11 | |
| Rest Experimental | 1.7 | |
| Rest Other | 6.3 | |

Top potential actionable events — 216 Patients

Legend: FDA Approved / Drug Repurposing / Experimental/Other Guidelines / Other

## Germline Predisposition

### # Events

Germline drivers: 84% None, 16% 1+

| Gene | Type | Urothelial tract (%) | Pan-Cancer (%) |
|---|---|---|---|
| CHEK2 | TSG | 3.8 | 3.2 |
| ATM | TSG | 1.3 | 1 |
| MITF | ONC | 1.3 | 0.7 |
| MSH6 | TSG | 1.3 | 0.4 |
| BRCA1 | TSG | 0.8 | 1.1 |
| BRCA2 | TSG | 0.8 | 1.5 |
| MLH1 | TSG | 0.8 | 0.2 |
| MSH2 | TSG | 0.8 | 1 |
| NTHL1 | TSG | 0.8 | 0.4 |

Top potential germline drivers — 28 Patients

Legend: STRUCTURAL_VARIANT / SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved / Drug Repurposing / Other / Experimental/Other Guidelines / None

### Highest evidence level treatment option identified by test strategy

| Test strategy | | | | | |
|---|---|---|---|---|---|
| WGS | 102 | 63 | 32 | 20 | 22 |
| Comprehensive 521 gene panel | 98 | 52 | 33 | 27 | 29 |
| Targeted 50 gene panel | 32 | 59 | 16 | 45 | 87 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.5 | 0.73 | 0.41 | 1.2 | 2.8 |
| Comprehensive 521 gene panel | 0.48 | 0.6 | 0.34 | 1 | 2.4 |
| Targeted 50 gene panel | 0.34 | 0.46 | | 1.1 | |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
- Fusion: 4
- HMZ Disruption: 1
- Partial CN Loss: 1

Drug Repurposing:
- HRD: 18
- Partial CN Loss: 6
- Fusion: 4
- HMZ Disruption: 2

Experimental/Other Guidelines:
- Partial CN Loss: 17

Other:
- Partial CN Loss: 34
- Small Variant: 5
- Full CN Loss: 4
- HMZ Disruption: 2

### Top missed events by Targeted Panel vs WGS

FDA Approved:
- TMB High: 76
- Fusion: 4
- Small Variant: 4
- HMZ Disruption: 1
- Partial CN Loss: 1

Drug Repurposing:
- Small Variant: 52
- HRD: 18
- Splice Site: 8
- Partial CN Loss: 6
- Fusion: 4

Experimental/Other Guidelines:
- Full CN Gain: 36
- Partial CN Loss: 17
- Small Variant: 9
- Full CN Loss: 4
- Partial CN Gain: 3

Other:
- Small Variant: 126
- Partial CN Loss: 34
- Splice Site: 10
- Full CN Loss: 4
- HMZ Disruption: 2

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Bladder Urothelial Carcinoma

## Cohort Metadata

### Data availability

**Number of patients with data**



### Patients with treatment and response data

Post-biopsy treatment / Responders



## Tumor Characteristics

■ Urothelial Tract  ■ Pan-Cancer



## Mutational Landscape

### Tumor purity / Clonal mutation fraction / Tumor mutational burden



### Variant types

SNV / INDEL / Structural / MNV



### Telomere Length / VDJ CDR3 Sequences / Microsatellite instability



### Mean genome ploidy / Aneuploidy Score / % Copy number alteration / % Genome LOH



## Processes Underlying Mutations



APOBEC: 41%
Chemical exposure: 14%
DNA damage repair: 14%
Tobacco: 5%
UV light: 4%
Ageing: 4%
Unknown: 19%

**Urothelial Tract 186 Patients**
**Pan-Cancer 6790 Patients**

Urothelial tract

## Copy Number Alteration Profile



## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers



■ AMPLIFICATION  ■ DELETION  ■ MUTATION  ■ FUSION

183 Patients

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events



166 Patients

■ FDA Approved  ■ Drug Repurposing  ■ Experimental/Other Guidelines  ■ Other

## Germline Predisposition

### # Events / Summary / Top potential germline drivers



21 Patients

■ STRUCTURAL_VARIANT  ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved  ■ Drug Repurposing  ■ Other  □ None

### Highest evidence level treatment option identified by test strategy



# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy



Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS



Number of Missed Events

### Top missed events by Targeted Panel vs WGS



Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Urothelial Non-Bladder Cancer

## Cohort Metadata

### Data availability

Number of patients with data



### Patients with treatment and response data

Post-biopsy treatment / Responders



## Tumor Characteristics

- UT Other
- Pan-Cancer



## Mutational Landscape

### Tumor purity / Clonal mutation fraction / Tumor mutational burden



### Variant types

SNV / INDEL / Structural / MNV



### Telomere Length / VDJ CDR3 Sequences / Microsatellite instability



### Mean genome ploidy / Aneuploidy Score / % Copy number alteration / % Genome LOH



## Processes Underlying Mutations

DNA damage repair: 29%
APOBEC: 27%
Ageing: 12%
Chemical exposure: 9%
Tobacco: 2%
UV light: 1%
Unknown: 20%

UT Other
52 Patients

Pan-Cancer
6790 Patients

Urothelial tract



## Copy Number Alteration Profile
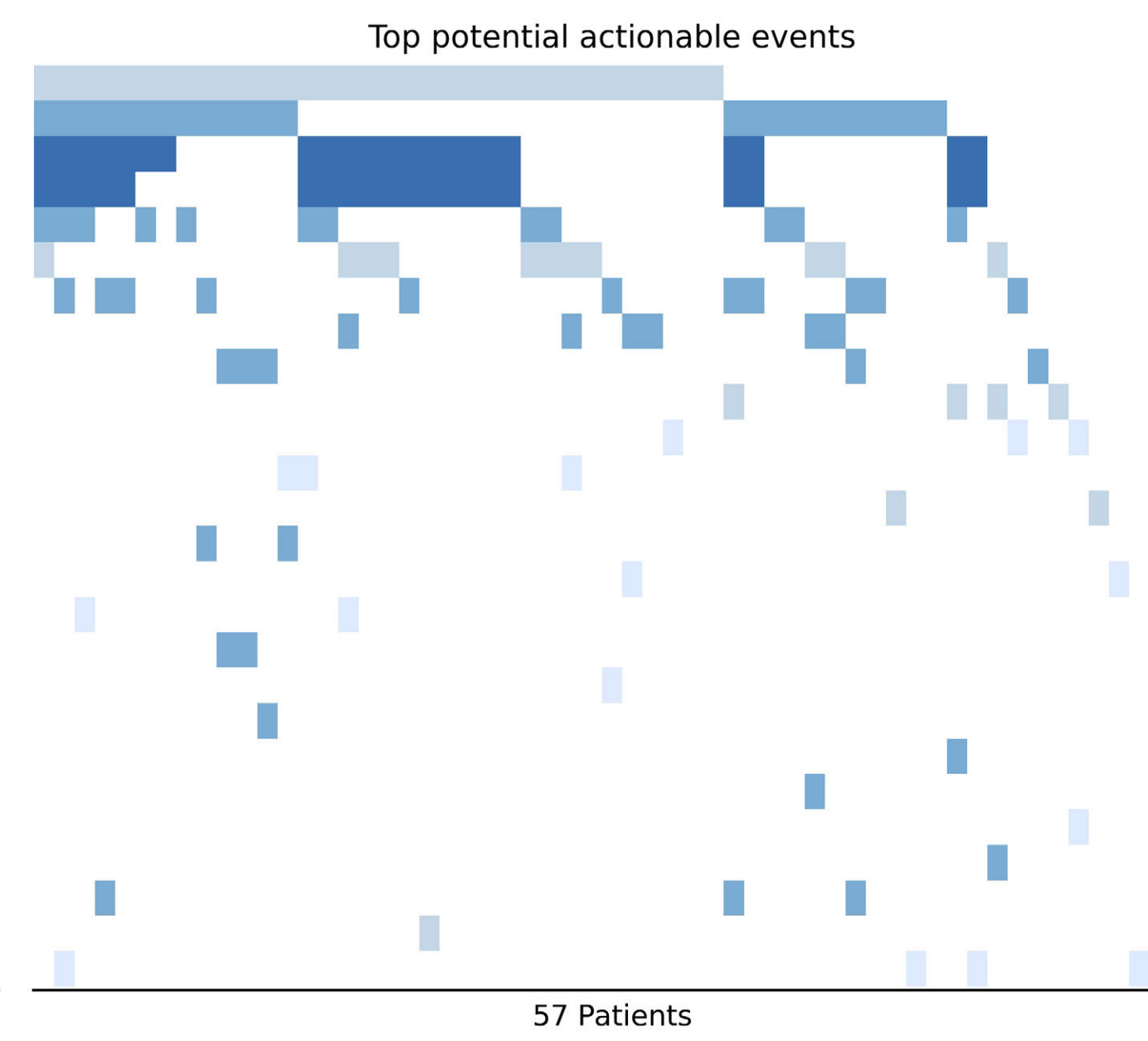


## Cancer Driver Landscape

### # Events / Summary / Top cancer drivers



Legend: AMPLIFICATION, DELETION, MUTATION, FUSION

52 Patients

## Potentially Actionable Events

### # Events / Summary / Top potential actionable events



Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

50 Patients

## Germline Predisposition

### # Events / Summary / Top potential germline drivers



Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

9 Patients

## WGS vs Panel Coverage

- FDA Approved
- Drug Repurposing
- Other
- Experimental/Other Guidelines
- None

### Highest evidence level treatment option identified by test strategy



# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy



Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS



Number of Missed Events

### Top missed events by Targeted Panel vs WGS



Number of Missed Events

# The Genomic And Actionability Landscape Of Uterine Carcinoma

**Hartwig** MEDICAL FOUNDATION

## Cohort Metadata

### Data availability
Number of patients with data

| | |
|---|---|
| WGS | 63 |
| RNASeq | 38 |
| Age, Sex | 41 |
| Biopsy site | 33 |
| Pretreatment | 17 |
| Treatment | 17 → |
| Response | 15 → |

### Patients with treatment and response data

Post-biopsy treatment / Responders

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 13 | 8 (62%) |
| Multiple | 1 | 1 (100%) |
| Targeted | 0 | |
| Hormonal | 1 | 1 (100%) |
| Immuno | 0 | |
| Radio | 2 | 2 (100%) |
| Other | 0 | |
| None or NA | 0 | |

## Tumor Characteristics

■ Uterus UCEC  ■ Pan-Cancer

| | Uterus UCEC | Pan-Cancer |
|---|---|---|
| TMB High | 23% | 21% |
| MSI High | 19% | 2% |
| WGD | 37% | 56% |
| Diploid Proportion | 45% | 34% |
| GIE HLA LOH | 12% | 19% |
| GIE Overall | 31% | 26% |
| Viral Insertions | 0% | 3% |
| HRD | 10% | 6% |

## Mutational Landscape

### Tumor purity
62% / 55%

### Clonal mutation fraction
86% / 95%

### Tumor mutational burden
4.4 — 23% High
4.2 — 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| | 10,846 / 10,737 | 1,289 / 983 | 183 / 109 | 150 / 92 |

Number of variants vs Quantile

### Telomere Length
0.68 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
6 / 6
Log2 (CDR3 + 1)

### Microsatellite instability
0.26 — 19% Instable
0.15 — 2%
MS indels per megabase

### Mean genome ploidy
2.1 / 2.6

### Aneuploidy Score
10 / 16

### % Copy number alteration
37% / 54%

### % Genome LOH
11% / 24%

## Processes Underlying Mutations

- DNA damage repair: 55%
- Ageing: 5%
- Chemical exposure: 4%
- UV light: 2%
- APOBEC: 1%
- Tobacco: 1%
- Unknown: 33%

Uterus UCEC — 63 Patients
Pan-Cancer — 6790 Patients

Uterus

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## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary — Top cancer drivers

Somatic drivers: 51% 6+ / 6+ 44%; 49% 1-5 / 1-5 54%
Oncogenes: 14% None / None 18%; 32% 3+ / 3+ 32%; 54% 1-2 / 1-2 50%
TSGs: 73% 3+ / 3+ 61%; 25% 1-2 / 1-2 33% (None)

| Gene | Type | Uterus UCEC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| PTEN | TSG | 54 | 14 | ▲ |
| TP53 | TSG | 44 | 55 | ▼ |
| ARID1A | TSG | 40 | 6 | ▲ |
| PIK3CA | ONC | 38 | 13 | ▲ |
| CTNNB1 | ONC | 19 | 2.9 | ▲ |
| FGFR2 | ONC | 19 | 1.2 | ▲ |
| KRAS | ONC | 19 | 15 | |
| PIK3R1 | TSG | 17 | 1.7 | ▲ |
| DMD | TSG | 13 | 3.5 | ▲ |
| ARID1B | TSG | 9.5 | 1.2 | ▲ |
| FBXW7 | TSG | 9.5 | 2.8 | ▲ |
| NF1 | TSG | 9.5 | 5 | |
| AR | ONC | 7.9 | 5.6 | |
| PPP2R1A | ONC | 7.9 | 0.3 | ▲ |
| AKT1 | ONC | 6.3 | 1.6 | ▲ |
| ATM | TSG | 6.3 | 2.9 | |
| B2M | TSG | 6.3 | 1.9 | ▲ |
| CCNE1 | ONC | 6.3 | 2.4 | |
| JAK1 | TSG | 6.3 | 1.1 | ▲ |
| LRP1B | TSG | 6.3 | 2.1 | |
| MECOM | ONC | 6.3 | 0.8 | ▲ |
| RB1 | TSG | 6.3 | 11 | |
| CBFB | TSG | 4.8 | 0.9 | ▲ |
| CDKN2A | TSG | 4.8 | 25 | ▼ |
| KMT2D | TSG | 4.8 | 2.9 | |
| MGA | TSG | 4.8 | 1.5 | ▲ |
| MYC | ONC | 4.8 | 5.7 | |
| RASA1 | TSG | 4.8 | 1.3 | ▲ |
| RPL22 | TSG | 4.8 | 0.9 | ▲ |

62 Patients

■ AMPLIFICATION  ■ DELETION  ■ MUTATION

## Potentially Actionable Events

### # Events / Summary — Top potential actionable events

Actionable: 10% None / None 18%; 59% 3+ / 3+ 26%; 32% 1-2 / 1-2 56%
Best treatment option: 10% None / None 18%; 8% Oth 14%; 10% Exp / Exp 5%; 38% Off / Off 28%; 35% FDA / FDA 36%

| Gene | Uterus UCEC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PTEN | 54 | 13 | |
| PIK3CA | 38 | 13 | |
| TMB High | 35 | 21 | |
| MSI High | 32 | 3.1 | |
| FGFR2 | 19 | 1.1 | ▲ |
| CTNNB1 | 17 | 2.7 | ▲ |
| KRAS | 17 | 14 | |
| ATM | 9.5 | 3.5 | ▲ |
| HR deficiency | 7.9 | 5.8 | |
| AKT1 | 6.3 | 1.4 | ▲ |
| CDKN2A | 4.8 | 24 | ▼ |
| KMT2D | 4.8 | 2.9 | |
| CCNE1 | 3.2 | 0.2 | ▲ |
| CHEK2 | 3.2 | 3 | |
| FGFR1 | 3.2 | 3.8 | |
| MTOR | 3.2 | 0.4 | ▲ |
| PALB2 | 3.2 | 0.2 | ▲ |
| AR | 1.6 | 2.8 | |
| BRCA1 | 1.6 | 1.3 | |
| BRIP1 | 1.6 | 0.4 | ▲ |
| CD274 | 1.6 | 0.5 | |
| EGFR | 1.6 | 5.1 | ▼ |
| ESR1 | 1.6 | 2.3 | |
| Rest Repurpose | 4.8 | | |
| Rest Experimental | 1.6 | | |
| Rest Other | 9.5 | | |

57 Patients

■ FDA Approved  ■ Drug Repurposing  ■ Experimental/Other Guidelines  ■ Other

## Germline Predisposition

### # Events / Summary — Top potential germline drivers

Germline drivers: 86% None / None 84%; 14% 1+ / 1+ 16%

| Gene | Type | Uterus UCEC (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRIP1 | TSG | 3.2 | 0.2 | ▲ |
| PALB2 | TSG | 3.2 | 0.3 | ▲ |
| ATM | TSG | 1.6 | 1 | |
| BRCA1 | TSG | 1.6 | 1.1 | |
| CHEK2 | TSG | 1.6 | 3.2 | |
| RAD51D | TSG | 1.6 | 0.4 | ▲ |
| RAD54L | TSG | 1.6 | 0.4 | ▲ |
| TP53 | TSG | 1.6 | 0.5 | ▲ |
| TSC1 | TSG | 1.6 | 0.1 | ▲ |

9 Patients

■ STRUCTURAL_VARIANT  ■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved  ■ Drug Repurposing  ■ Other  ■ Experimental/Other Guidelines  □ None

### Highest evidence level treatment option identified by test strategy

| Test strategy | FDA Approved | Drug Repurposing | Exp/Other | Other | None |
|---|---|---|---|---|---|
| WGS | 22 | 24 | 12 | 2 | 3 |
| Comprehensive 521 gene panel | 22 | 21 | 13 | 2 | 5 |
| Targeted 50 gene panel | 20 | 21 | 11 | | 11 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.67 | 1.2 | 1.5 | 0.35 | 3.7 |
| Comprehensive 521 gene panel | 0.67 | 1.1 | 1.4 | 0.25 | 3.4 |
| Targeted 50 gene panel | 0.32 | 0.78 | 0.97 | | 2.1 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

FDA Approved:
Drug Repurposing: HRD 5; Partial CN Loss 3
Experimental/Other Guidelines: Partial CN Loss 3; Partial CN Gain 2; Small Variant 1
Other: Partial CN Loss 5; Small Variant 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

FDA Approved: TMB High 22
Drug Repurposing: Small Variant 18; HRD 5; Partial CN Loss 3; Splice Site 2
Experimental/Other Guidelines: Small Variant 19; Full CN Gain 5; Partial CN Loss 3; Full CN Loss 2; Partial CN Gain 2
Other: Small Variant 12; Partial CN Loss 5; Full CN Loss 2; Splice Site 1

Number of Missed Events

# The Genomic And Actionability Landscape Of Uterine Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 138 |
| RNASeq | 78 |
| Age, Sex | 88 |
| Biopsy site | 75 |
| Pretreatment | 55 |
| Treatment | 49 → |
| Response | 42 → |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | Post-biopsy treatment | Responders |
|---|---|---|
| Chemo | 34 | 17 (50%) |
| Multiple | 5 | 5 (100%) |
| Targeted | 1 | 0 |
| Hormonal | 1 | 1 (100%) |
| Immuno | 2 | 0 |
| Radio | 10 | 6 (60%) |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

Legend: Uterus, Pan-Cancer

| | Uterus | Pan-Cancer |
|---|---|---|
| TMB High | 17% | 21% |
| MSI High | 10% | 2% |
| WGD | 47% | 56% |
| Diploid Proportion | 38% | 34% |
| GIE HLA LOH | 26% | 19% |
| GIE Overall | 40% | 26% |
| Viral Insertions | 44% | 3% |
| HRD | 7% | 6% |

## Mutational Landscape

**Tumor purity** — 62%, 55%

**Clonal mutation fraction** — 90%, 95%

**Tumor mutational burden** — 4.8, 4.2; High 17%, 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Uterus | 11,704 | 1,032 | 183 | 152 |
| Pan-Cancer | 10,846 | 983 | 146 | 92 |

Number of variants / Quantile

**Telomere Length** — 0.75, 0.82
Log2 (Tumor/Germline length)

**VDJ CDR3 Sequences** — 6, 6
Log2 (CDR3 + 1)

**Microsatellite instability** — 0.16, 0.15; Instable 10%, 2%
MS indels per megabase

**Mean genome ploidy** — 2.3, 2.6

**Aneuploidy Score** — 13, 16

**% Copy number alteration** — 41%, 54%

**% Genome LOH** — 19%, 24%

## Processes Underlying Mutations

| | |
|---|---|
| DNA damage repair: | 47% |
| APOBEC: | 8% |
| Chemical exposure: | 6% |
| Ageing: | 6% |
| UV light: | 2% |
| Tobacco: | 1% |
| Unknown: | 30% |

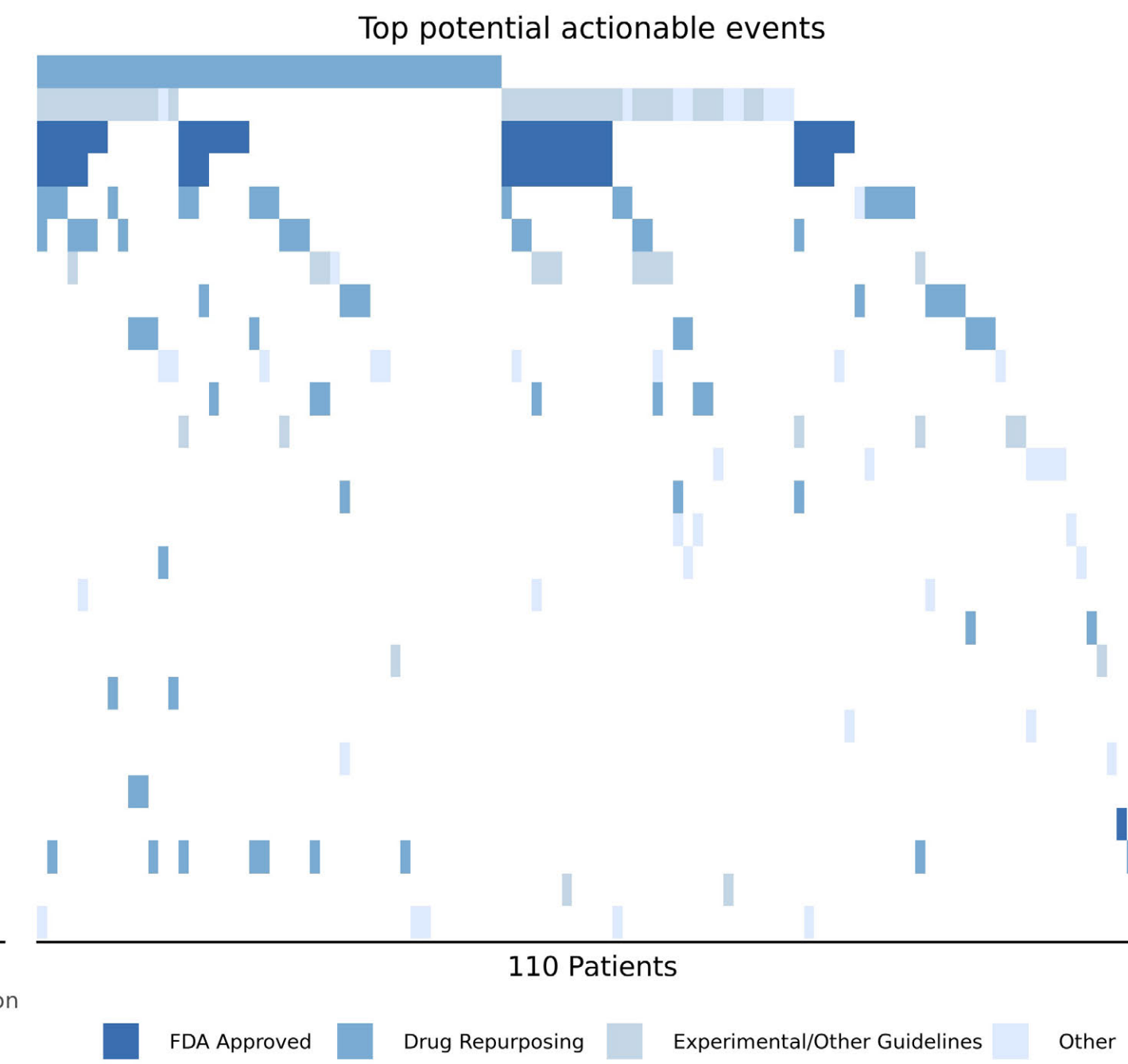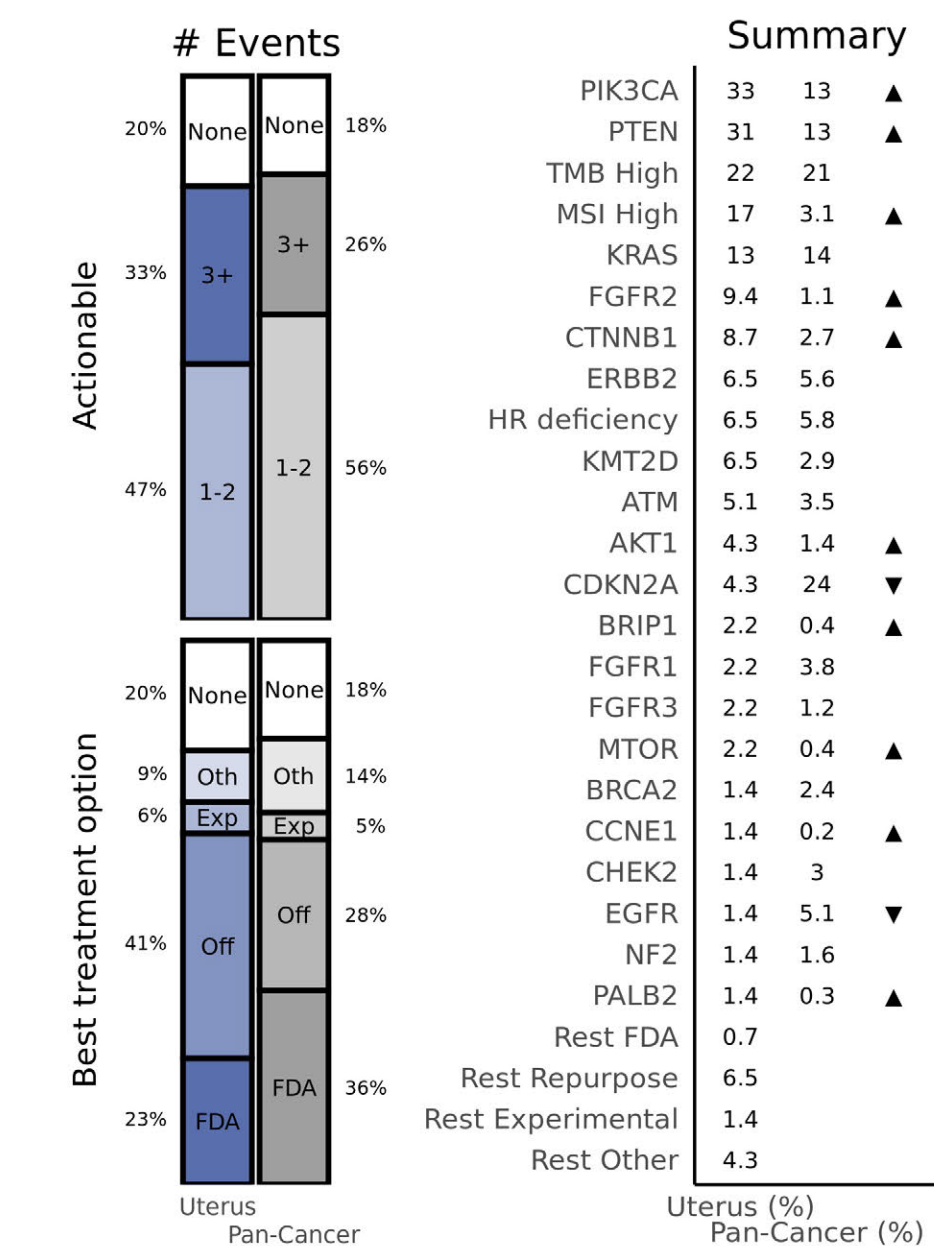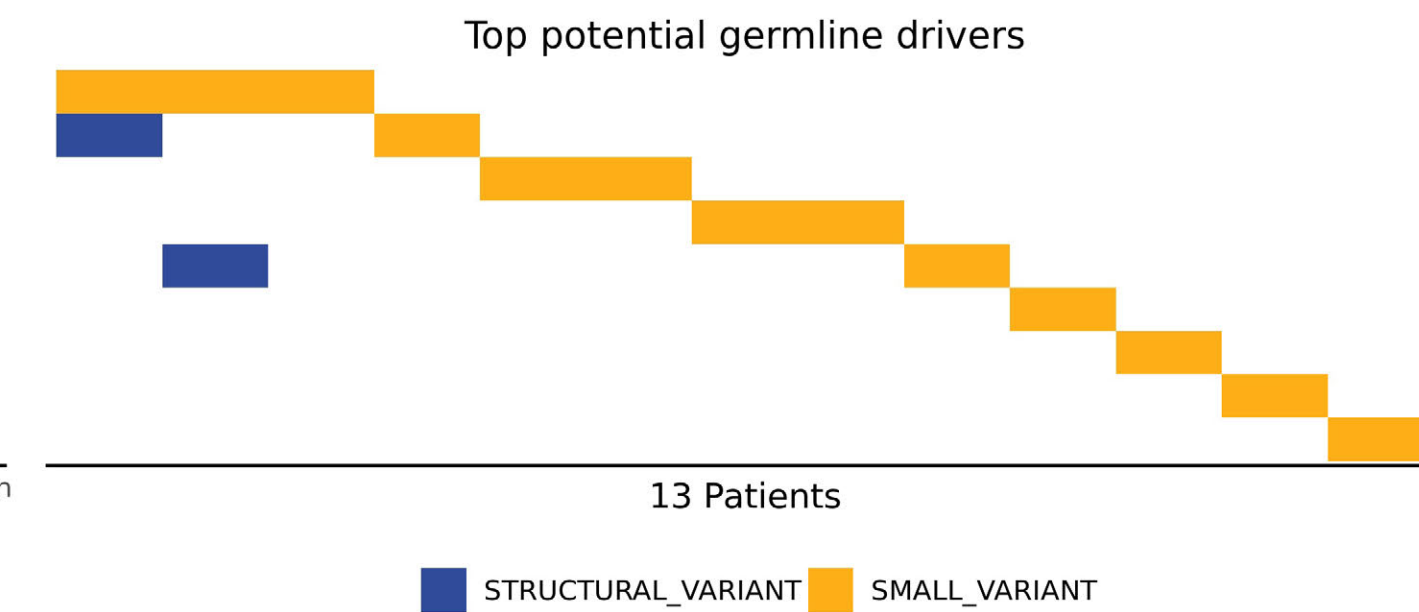Uterus — 138 Patients
Pan-Cancer — 6790 Patients

Uterus

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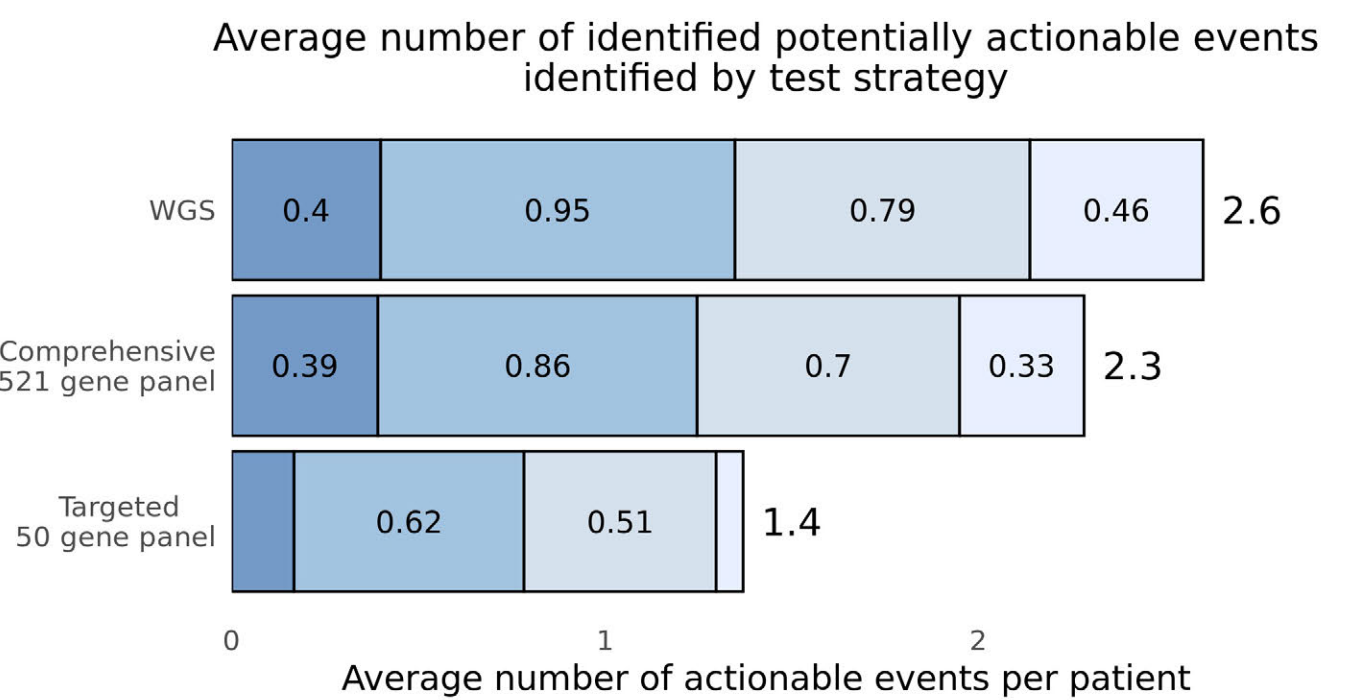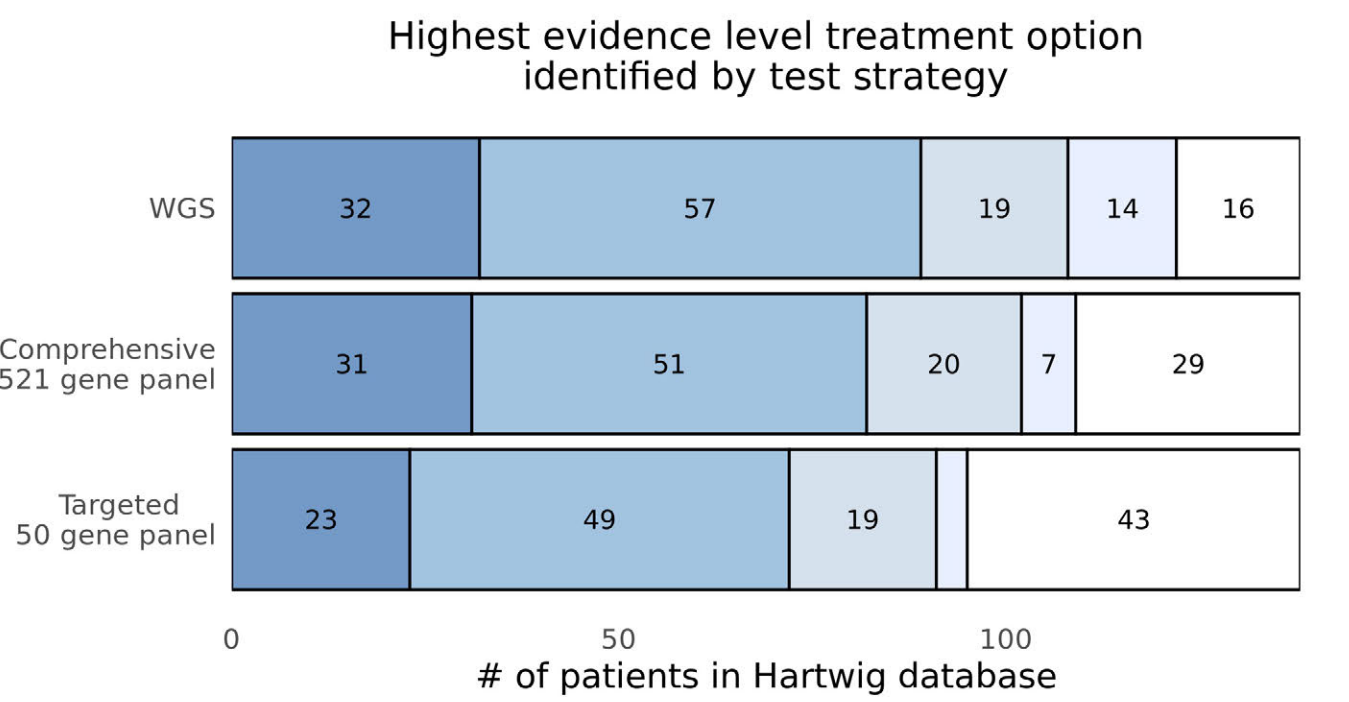
## Copy Number Alteration Profile



## Cancer Driver Landscape

### Top cancer drivers



| Gene | Type | Uterus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 35 | 55 | ▼ |
| PIK3CA | TSG | 33 | 13 | ▲ |
| PTEN | TSG | 31 | 14 | ▲ |
| ARID1A | TSG | 20 | 6 | ▲ |
| KRAS | ONC | 14 | 15 | |
| STK11 | TSG | 12 | 4.1 | ▲ |
| FBXW7 | TSG | 12 | 2.8 | ▲ |
| CTNNB1 | ONC | 10 | 2.9 | ▲ |
| FGFR2 | ONC | 9.4 | 1.2 | ▲ |
| PIK3R1 | ONC | 9.4 | 1.7 | ▲ |
| TERT | ONC | 8 | 13 | |
| CCNE1 | ONC | 7.2 | 2.4 | ▲ |
| LRP1B | TSG | 7.2 | 2.1 | ▲ |
| RB1 | TSG | 7.2 | 11 | |
| DMD | TSG | 6.5 | 3.5 | |
| ERBB2 | ONC | 6.5 | 5.7 | |
| KMT2C | TSG | 6.5 | 3.7 | |
| KMT2D | TSG | 6.5 | 2.9 | |
| NF1 | TSG | 6.5 | 5 | |
| ARID1B | TSG | 5.8 | 1.2 | ▲ |
| TGFBR2 | TSG | 5.8 | 2.7 | |
| AKT1 | ONC | 5.1 | 1.6 | ▲ |
| B2M | TSG | 4.3 | 1.9 | |
| CDKN2A | TSG | 4.3 | 25 | ▼ |
| EP300 | TSG | 4.3 | 1.3 | ▲ |
| MECOM | ONC | 4.3 | 0.8 | ▲ |
| MYC | ONC | 4.3 | 5.7 | |
| AR | ONC | 3.6 | 5.6 | |
| ATM | TSG | 3.6 | 2.9 | |

**Somatic drivers** — 38% 6+ (6+) 44%; 59% 1-5 (1-5) 54%

**Oncogenes** — 21% None (None) 18%; 31% 3+ (3+) 32%; 48% 1-2 (1-2) 50%

**TSGs** — 7% None (None) 6%; 62% 3+ (3+) 61%; 32% 1-2 (1-2) 33%

128 Patients

Legend: AMPLIFICATION, DELETION, MUTATION

## Potentially Actionable Events

### Top potential actionable events



| Event | Uterus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|
| PIK3CA | 33 | 13 | ▲ |
| PTEN | 31 | 13 | ▲ |
| TMB High | 22 | 21 | |
| MSI High | 17 | 3.1 | ▲ |
| KRAS | 13 | 14 | |
| FGFR2 | 9.4 | 1.1 | ▲ |
| CTNNB1 | 8.7 | 2.7 | ▲ |
| ERBB2 | 6.5 | 5.6 | |
| HR deficiency | 6.5 | 5.8 | |
| KMT2D | 6.5 | 2.9 | |
| ATM | 5.1 | 3.5 | |
| AKT1 | 4.3 | 1.4 | ▲ |
| CDKN2A | 4.3 | 24 | ▼ |
| BRIP1 | 2.2 | 0.4 | ▲ |
| FGFR1 | 2.2 | 3.8 | |
| FGFR3 | 2.2 | 1.2 | |
| MTOR | 2.2 | 0.4 | |
| BRCA2 | 1.4 | 2.4 | |
| CCNE1 | 1.4 | 0.2 | |
| CHEK2 | 1.4 | 3 | |
| EGFR | 1.4 | 5.1 | ▼ |
| NF2 | 1.4 | 1.6 | |
| PALB2 | 1.4 | 0.3 | ▲ |
| Rest FDA | 0.7 | | |
| Rest Repurpose | 6.5 | | |
| Rest Experimental | 1.4 | | |
| Rest Other | 4.3 | | |

**Actionable** — 20% None (None) 18%; 33% 3+ (3+) 26%; 47% 1-2 (1-2) 56%

**Best treatment option** — 20% None (None) 18%; 9% Oth (Oth) 14%; 6% Exp (Exp) 5%; 41% Off (Off) 28%; 23% FDA (FDA) 36%

110 Patients

Legend: FDA Approved, Drug Repurposing, Experimental/Other Guidelines, Other

## Germline Predisposition

### Top potential germline drivers



| Gene | Type | Uterus (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| ATM | TSG | 2.2 | 1 | |
| BRIP1 | TSG | 1.4 | 0.2 | ▲ |
| MSH2 | TSG | 1.4 | 1 | |
| PALB2 | TSG | 1.4 | 0.3 | ▲ |
| POLD1 | TSG | 1.4 | 0.1 | ▲ |
| BRCA1 | TSG | 0.7 | 1.5 | |
| BRCA2 | TSG | 0.7 | 1.5 | |
| CHEK2 | TSG | 0.7 | 3.2 | ▼ |
| MUTYH | TSG | 0.7 | 1.9 | |

**Germline drivers** — 87% None (None) 84%; 13% 1+ (1+) 16%

13 Patients

Legend: STRUCTURAL_VARIANT, SMALL_VARIANT

## WGS vs Panel Coverage

Legend: FDA Approved, Drug Repurposing, Other, Experimental/Other Guidelines, None

### Highest evidence level treatment option identified by test strategy

| Test strategy | | | | | |
|---|---|---|---|---|---|
| WGS | 32 | 57 | 19 | 14 | 16 |
| Comprehensive 521 gene panel | 31 | 51 | 20 | 7 | 29 |
| Targeted 50 gene panel | 23 | 49 | 19 | 43 | |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| Test strategy | | | | | Total |
|---|---|---|---|---|---|
| WGS | 0.4 | 0.95 | 0.79 | 0.46 | 2.6 |
| Comprehensive 521 gene panel | 0.39 | 0.86 | 0.7 | 0.33 | 2.3 |
| Targeted 50 gene panel | 0.62 | 0.51 | | | 1.4 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved**
- Fusion: 1

**Drug Repurposing**
- HRD: 9
- Partial CN Loss: 3
- HMZ Disruption: 1

**Experimental/Other Guidelines**
- Partial CN Loss: 8
- Partial CN Gain: 2
- Small Variant: 1

**Other**
- Partial CN Loss: 16
- Small Variant: 1
- Full CN Loss: 1

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved**
- TMB High: 31
- Fusion: 1

**Drug Repurposing**
- Small Variant: 31
- HRD: 9
- Partial CN Loss: 3
- Splice Site: 2
- HMZ Disruption: 1

**Experimental/Other Guidelines**
- Small Variant: 19
- Partial CN Loss: 8
- Full CN Gain: 7
- Full CN Loss: 2
- Partial CN Gain: 2

**Other**
- Small Variant: 33
- Partial CN Loss: 16
- Full CN Loss: 3
- Splice Site: 2

Number of Missed Events

## Panel annotations and abbreviations

# The Genomic And Actionability Landscape Of Vulva Cancer

## Cohort Metadata

### Data availability

**Number of patients with data**

| | |
|---|---|
| WGS | 17 |
| RNASeq | 8 |
| Age, Sex | 7 |
| Biopsy site | 6 |
| Pretreatment | 7 |
| Treatment | 7 |
| Response | 4 |

### Patients with treatment and response data

**Post-biopsy treatment** / **Responders**

| | Treatment | Responders |
|---|---|---|
| Chemo | 3 | 0 |
| Multiple | 0 | 0 |
| Targeted | 0 | 0 |
| Hormonal | 0 | 0 |
| Immuno | 1 | 0 |
| Radio | 2 | 0 |
| Other | 0 | 0 |
| None or NA | 0 | 0 |

## Tumor Characteristics

**Vulva** ■ **Pan-Cancer** ■

| | Vulva | Pan-Cancer |
|---|---|---|
| TMB High | 6% | 21% |
| MSI High | 0% | 2% |
| WGD | 44% | 56% |
| Diploid Proportion | 38% | 34% |
| GIE HLA LOH | 19% | 19% |
| GIE Overall | 44% | 26% |
| Viral Insertions | 31% | 3% |
| HRD | 0% | 6% |

## Mutational Landscape

### Tumor purity
50% / 55%

### Clonal mutation fraction
95% / 95%

### Tumor mutational burden
4.6 / 6% High / 4.2 / 21%
TMB per Megabase

### Variant types

| | SNV | INDEL | Structural | MNV |
|---|---|---|---|---|
| Vulva | 11,955 | 1,136 | 183 | 92 |
| Pan-Cancer | 10,846 | 983 | 152 | 77 |

Number of variants — Quantile

### Telomere Length
0.92 / 0.82
Log2 (Tumor/Germline length)

### VDJ CDR3 Sequences
12 / 6

### Microsatellite instability
0.23 / 0% / Instable / 0.15 / 2%
MS indels per megabase

### Mean genome ploidy
2.2 / 2.6

### Aneuploidy Score
10 / 16

### % Copy number alteration
37% / 54%

### % Genome LOH
20% / 24%

## Processes Underlying Mutations

- APOBEC: 34%
- DNA damage repair: 11%
- Chemical exposure: 10%
- Ageing: 8%
- UV light: 3%
- Tobacco: 2%
- Unknown: 33%

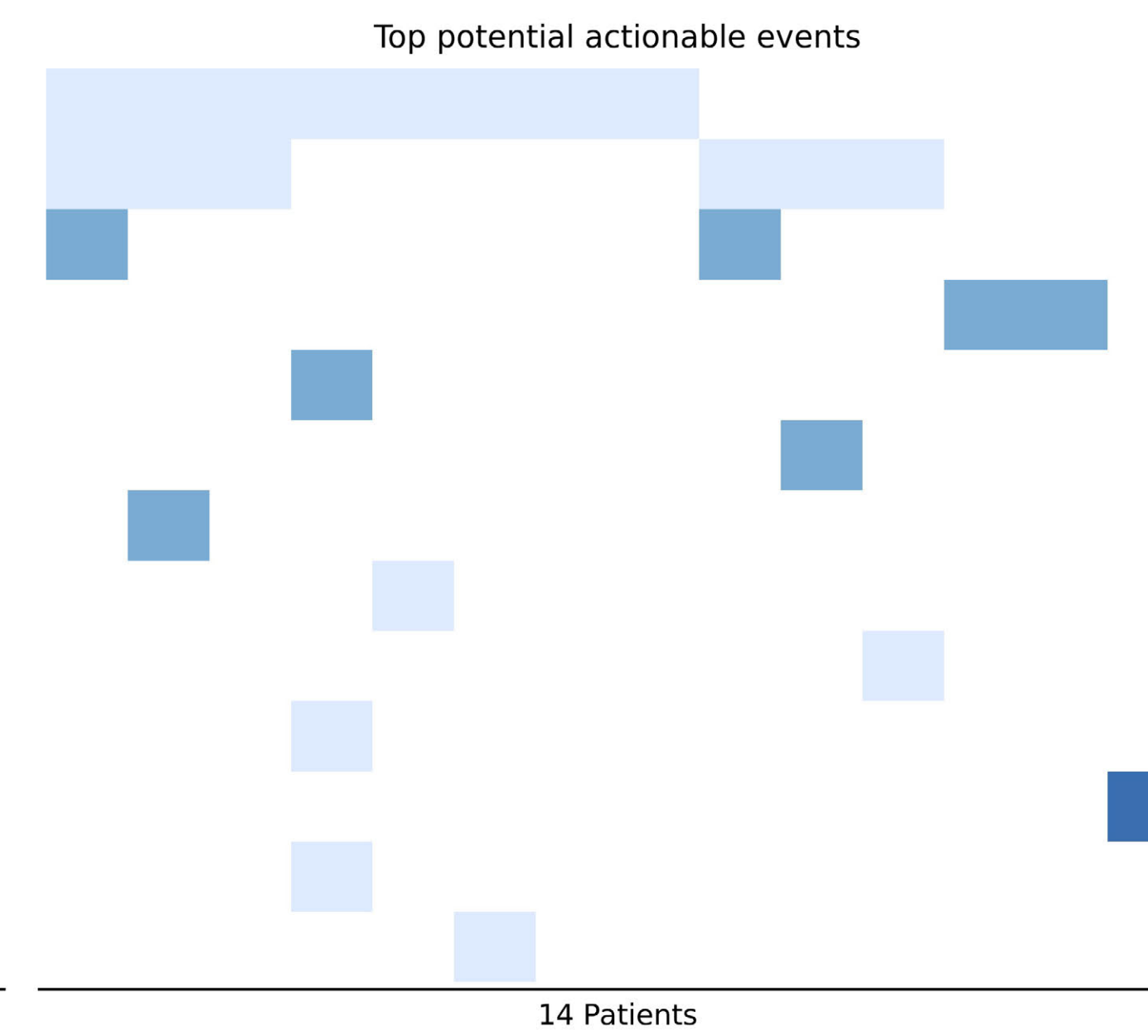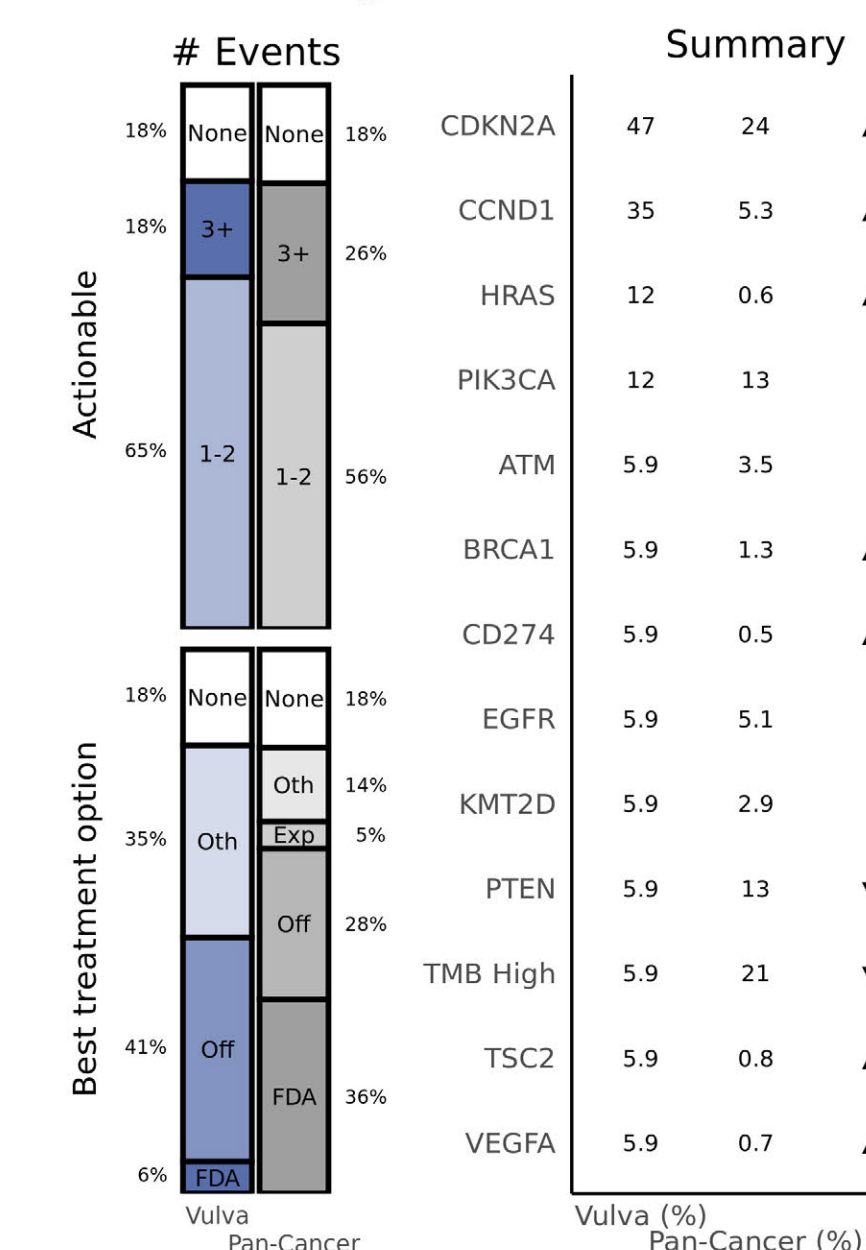**Vulva** 17 Patients
**Pan-Cancer** 6790 Patients

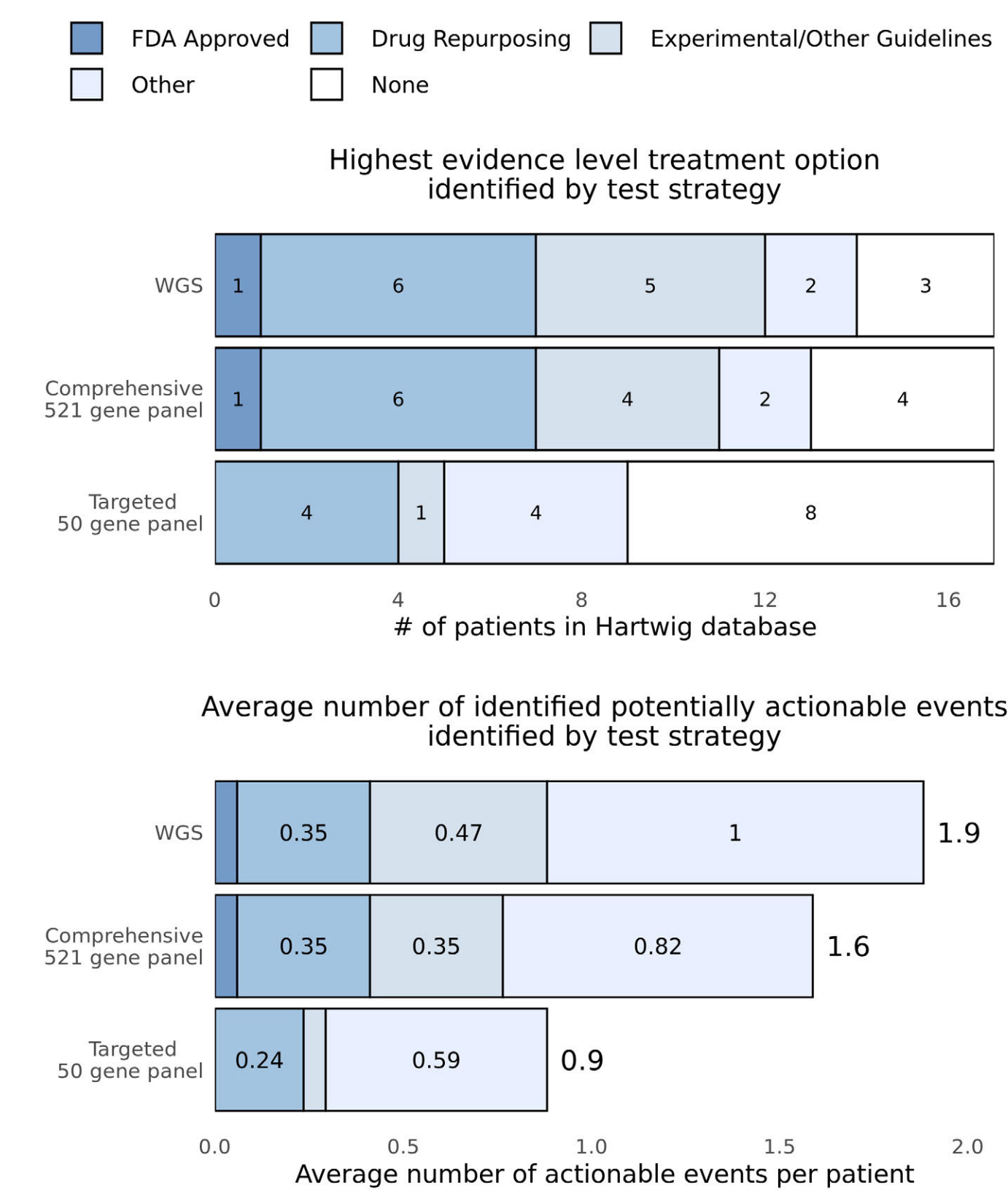Vulva

## Copy Number Alteration Profile

## Cancer Driver Landscape

### # Events / Summary

| | Type | Vulva (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| TP53 | TSG | 76 | 55 | ▲ |
| CDKN2A | TSG | 59 | 25 | ▲ |
| TERT | ONC | 47 | 13 | ▲ |
| CCND1 | ONC | 35 | 5.6 | ▲ |
| FGF3 | ONC | 35 | 5.2 | ▲ |
| FAT1 | TSG | 24 | 1.5 | ▲ |
| PTPRD | TSG | 24 | 3 | ▲ |
| HRAS | ONC | 18 | 0.7 | ▲ |
| SMAD4 | TSG | 18 | 8 | ▲ |
| ATRX | TSG | 12 | 2.4 | ▲ |
| CASP8 | TSG | 12 | 1 | ▲ |
| CD44 | ONC | 12 | 0.6 | ▲ |
| CTCF | TSG | 12 | 0.6 | ▲ |
| HLA-A | TSG | 12 | 0.7 | ▲ |
| PIK3CA | ONC | 12 | 13 | |
| SMAD2 | TSG | 12 | 1.2 | ▲ |
| ARID2 | TSG | 5.9 | 1.8 | ▲ |
| ATM | TSG | 5.9 | 2.9 | |
| B2M | TSG | 5.9 | 1.9 | |
| BCL9L | TSG | 5.9 | 0.6 | |
| CASZ1 | TSG | 5.9 | 0.5 | |
| CD274 | ONC | 5.9 | 0.6 | |
| CHD4 | ONC | 5.9 | 1.2 | |
| CREBBP | TSG | 5.9 | 1.9 | |
| CTNNA1 | TSG | 5.9 | 1 | |
| EGFR | ONC | 5.9 | 5.4 | |
| FBXW7 | TSG | 5.9 | 2.8 | |
| GPHN | TSG | 5.9 | 0.3 | ▲ |
| H3-3A | ONC | 5.9 | 0.3 | ▲ |

Somatic drivers: 59% / 44%; 41% / 54%
Oncogenes: 18% / 18%; 41% / 32%; 41% / 50%
TSGs: 65% / 61%; 35% / 33%

**Top cancer drivers** — 17 Patients

■ AMPLIFICATION ■ DELETION ■ MUTATION

## Potentially Actionable Events

### # Events / Summary

| | | Vulva (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| CDKN2A | | 47 | 24 | ▲ |
| CCND1 | | 35 | 5.3 | ▲ |
| HRAS | | 12 | 0.6 | ▲ |
| PIK3CA | | 12 | 13 | |
| ATM | | 5.9 | 3.5 | |
| BRCA1 | | 5.9 | 1.3 | ▲ |
| CD274 | | 5.9 | 0.5 | ▲ |
| EGFR | | 5.9 | 5.1 | |
| KMT2D | | 5.9 | 2.9 | |
| PTEN | | 5.9 | 13 | ▼ |
| TMB High | | 5.9 | 21 | ▼ |
| TSC2 | | 5.9 | 0.8 | ▲ |
| VEGFA | | 5.9 | 0.7 | ▲ |

Actionable: 18% / 18%; 18% / 26%; 65% / 56%
Best treatment option: 18% / 18%; 35% Oth / 14% Oth, Exp, Off; 41% Off / 28% Off; 6% FDA / 36% FDA

**Top potential actionable events** — 14 Patients

■ FDA Approved ■ Drug Repurposing ■ Other

## Germline Predisposition

### # Events / Summary

| | Type | Vulva (%) | Pan-Cancer (%) | Direction |
|---|---|---|---|---|
| BRCA1 | TSG | 5.9 | 1.1 | ▲ |
| RAD50 | TSG | 5.9 | 0.5 | ▲ |

Germline drivers: 88% None / 84% None; 12% / 16%

**Top potential germline drivers** — 2 Patients

■ SMALL_VARIANT

## WGS vs Panel Coverage

■ FDA Approved ■ Drug Repurposing ■ Other ■ None

### Highest evidence level treatment option identified by test strategy

| | FDA Approved | Drug Repurposing | Other | None |
|---|---|---|---|---|
| WGS | 1 | 6 | 5 | 2 / 3 |
| Comprehensive 521 gene panel | 1 | 6 | 4 | 2 / 4 |
| Targeted 50 gene panel | 4 | 1 | 4 | 8 |

# of patients in Hartwig database

### Average number of identified potentially actionable events identified by test strategy

| | | | | Total |
|---|---|---|---|---|
| WGS | 0.35 | 0.47 | 1 | 1.9 |
| Comprehensive 521 gene panel | 0.35 | 0.35 | 0.82 | 1.6 |
| Targeted 50 gene panel | 0.24 | 0.59 | | 0.9 |

Average number of actionable events per patient

### Top missed events by Comprehensive Panel vs WGS

**FDA Approved** / **Drug Repurposing**

**Experimental/Other Guidelines** / **Other**

| | |
|---|---|
| Full CN Gain | 1 |
| Partial CN Loss | 1 |
| Partial CN Loss | 3 |

Number of Missed Events

### Top missed events by Targeted Panel vs WGS

**FDA Approved** / **Drug Repurposing**

| | |
|---|---|
| TMB High | 1 |
| Small Variant | 2 |

**Experimental/Other Guidelines** / **Other**

| | |
|---|---|
| Full CN Gain | 6 |
| Partial CN Loss | 1 |
| Small Variant | 3 |
| Partial CN Loss | 3 |
| Full CN Gain | 1 |

Number of Missed Events

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